Université de Montréal

Machine Learning Analysis of Calcifications on CT-Scan to Predict Abdominal Aortic Aneurysm Rupture

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Résumé

Historique et Objectif : La littérature est conflictuelle sur le rôle des calcifications aortiques dans la rupture d'anévrisme de l'aorte abdominale (AAA). La prédiction de rupture d'AAA basée sur le sexe et le diamètre est peu précise. Le but de ce projet était donc de déterminer si les calcifications permettent de mieux prédire la rupture d'AAA que le sexe et le diamètre à eux seuls.

Méthodologie : Lors de cette étude rétrospective, 80 patients traités pour rupture d'AAA entre Janvier 2001 et Août 2018 ont été appariés à 80 patients non-rompus sur la base du diamètre maximal d'AAA, de l'âge, du sexe et de la présence de contraste lors du scan. La charge et la répartition des calcifications de la paroi aortique ainsi que certaines variables morphologiques d'anévrisme ont été comparées entre les deux groupes par analyse univariée et apprentissage machine.

Résultats : L'âge moyen des patients était de 74.0 ± 8.4 ans et 89% étaient des hommes. Les diamètres d'AAA étaient équivalents entre groupes (80.9 ± 17.5 vs 79.0 ± 17.3 mm, p= 0.505). Selon l'analyse univariée, les anévrismes rompus comportaient significativement moins d'agrégats de calcifications (18.0 ± 17.9 vs 25.6 ± 18.9, p=0.010) et étaient moins enclins à avoir un collet (45.0% vs 76.3%, p<0.0001). Les 5 variables les plus importantes délivrées par l'apprentissage machine étaient: collet, antiplaquettaires, nombre de calcifications, distance d'Euler entre calcifications et finalement l'écart-type de la distance d'Euler entre calcifications. Le modèle à 5 variables a produit une aire sous la courbe (AUC) de 0.81 ± 0.02 (sensibilité 83% et

spécificité 71%), supérieure à une AUC de 0.67(IC 95%, 0.58-0.77%) (sensibilité 60% et spécificité 77%) obtenues dans une étude antérieure avec une population similaire à celle-ci et ne tenant compte que du sexe et du diamètre.

Conclusion : La charge en calcifications des anévrismes rompus était moins bien répartie que celle des non-rompus. Le modèle d'apprentissage machine a mieux prédit la rupture que le modèle basé uniquement sur le diamètre et le sexe.

Mots-clés: CT scan, Calcifications, Anévrisme de l'aorte abdominale, Rupture, Apprentissage machine

Summary

Background and Purpose: Literature is conflictual regarding the role of aortic calcification in AAA rupture. AAA rupture prediction based on sex and diameter could be improved. The goal of this project was to assess whether aortic calcification could better predict AAA rupture.

Methods: In this retrospective study, 80 patients treated for a ruptured AAA between January 2001 and August 2018 were matched with 80 non-ruptured patients based on maximal AAA diameter, age, sex and contrast enhancement status of the CT scan. Calcification load and dispersion, morphologic and clinical variables were compared between both groups using a univariable analysis and machine learning.

Results: Mean age of patients was 74.0 ± 8.4 years and 89% were men. AAA diameters were equivalent in both groups (80.9 ± 17.5 vs 79.0 ± 17.3 mm, p= 0.505). Ruptured aneurysms contained a smaller number of calcification chunks than the non-ruptured (18.0 ± 17.9 vs 25.6 ± 18.9, p=0.010) and were less likely to have a proximal neck than the non-ruptured (45.0% vs 76.3%, p<0.0001). In the machine learning analysis, 5 variables were associated to AAA rupture: proximal neck, antiplatelets, calcification number, Euler distance between calcifications and standard deviation of the Euler distance between calcifications. The model including these 5 variables yielded an area under the curve (AUC) of 0.81 ± 0.02 (83% sensitivity and 71% specificity) which was better than a previous study with a similar population reporting a 0.67 AUC (95% CI, 0.58-0.77%) (60% sensitivity and 77% specificity) for sex and diameter only.

Conclusion: Ruptured aneurysms were more likely to have their calcification load concentrated in a small number of clusters closer to each other. Our 5-variable model predicted rupture better than the model based on age and sex.

Keywords: CT scan, Calcifications, Abdominal Aortic Aneurysm, Rupture, Machine Learning

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Abbreviations

AAA: Abdominal aortic aneurysm

AUC: Area under the curve

C+: Contrast-enhanced CT Scan

C-: Unenhanced CT Scan

CHUM: Centre Hospitalier de l'Université de Montréal

Dmax: maximal diameter

EVAR: Endovascular aortic repair

HU: Hounsfield Units

MUHC: McGill University Hospital Center

ROC: Receiving-operating characteristic

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Section 1 – Introduction

1.1 Abdominal Aortic Aneurysms

1.1.1 Epidemiology

Prevalence

Screening studies estimated the prevalence of AAA at about 1.4% in the population aged 50 to 84 in the United States (which corresponds to 1.1 million people)(4). In the population targeted by the USPSTF (United States Preventive Services Task Force) for AAA screening (men aged 65 to 75 with smoking history), the prevalence rises to 4.9% (4, 5).

However, the overwhelming majority of these AAAs are small, the prevalence of those AAAs measuring ≥5.5 cm only accounts for around 0.5% (6). The prevalence of AAA in women is much smaller than men as a study showed AAAs to be 6 times less prevalent in women aged 65-80 years old compared to men (1.3% vs 7.6%) (7). The prevalence of AAA increases with age in both men and women, albeit this tendency is more marked in men (8).

Incidence

AAA annual incidence in Norwegian and British studies corresponds to 2.5 to a maximum of 6.5 AAAs per 1000 person-years (9, 10). Age is significantly related to an increase in incidence (10, 11). However, AAA incidence appears to be decreasing nowadays. Indeed, various studies have revealed this new tendency, recording a 70% fall in incidence between the late 1980s-early 1990s and 2010s in the UK and Sweden (12-15). This fall in incidence could be caused by the overall reduction in smoking prevalence over time (16).

Mortality

AAA-related death is the 12−15th leading cause of death in the USA and Europe (17). In the United States, aortic aneurysms caused 9928 deaths in 2017 (18). The mortality for patients with ruptured AAA is still high, stalling at 80-90% and about half die before being admitted to the hospital. Untreated intra-abdominal hemorrhage caused by AAA rupture leads to 100% mortality(17). However, AAA-related mortality has decreased by almost 50% since the early 1990s. Short-term AAA-related deaths decreased by more than half (26.1 in 1995 to 12.1 in per 100,000 in 2008, P<0.001) (19).

1.1.2 Anatomy

Aneurysms consist in a segmental dilation of a blood vessel encompassing all three layers of the vessel (intima, media and adventitia). An AAA can be defined as an increment in diameter at least 50% greater than the normal aortic diameter (20). The average maximal diameter of the infrarenal aorta in adults is around 2.0 cm, the range of reported mean maximal abdominal aortic diameter by CT in a cohort of 260 age-matched patients was <3.0 cm (1.66-2.16 cm for women and 1.99-2.39 cm for men) (21). Therefore, an infrarenal aorta with a maximum diameter ≥3.0 cm is considered aneurysmal (20).

Abdominal aortic aneurysms can be classified in three categories: suprarenal (aneurysmal dilation of the aorta above renal arteries with or without involvement of renal arteries or celiac trunk, however not extending to the thoracic aorta), juxtarenal (aneurysmal dilation of aorta at the level of renal arteries with or without involvement of renal arteries) and infrarenal (below renal arteries) with a neck between renal arteries and the proximal portion of the AAA being the most common type (22, 23). AAAs can also be associated with iliac aneurysms and/or with thoracic aneurysms, becoming thoraco-abdominal aneurysms, which have their own classification. Also, AAAs can present as fusiform or saccular (24, 25).

1.1.3 AAA Pathogenesis

1.1.3.1 Susceptibility of the Infrarenal Aorta

Embryology

Smooth muscle cells of the infrarenal aorta wall stem from paraxial mesodermal somites (obsolete term: primitive segments) contrarily to other parts of the aorta and thus, appear to be more susceptible to aneurysmal degeneration (26).

Histology

There is a decreasing gradient of thickness and number of media elastic lamellae from the root of the aorta to the iliac bifurcation, the infrarenal aorta having the smallest number of elastic lamellae out of all aortic compartments (27). This trend is also observed with collagen, found scarcely in the infrarenal aorta compared to other parts (28). Vasa vasorum, which ensure the oxygen and nutrient supply of the external part of the aorta and coalesce in the adventitia, are sporadic in the infrarenal aorta (29, 30) (Figure 1).

Hemodynamics

The infrarenal aortic area is also affected by a greater aortic pulse wave amplitude from the heart towards the infrarenal aorta (31).

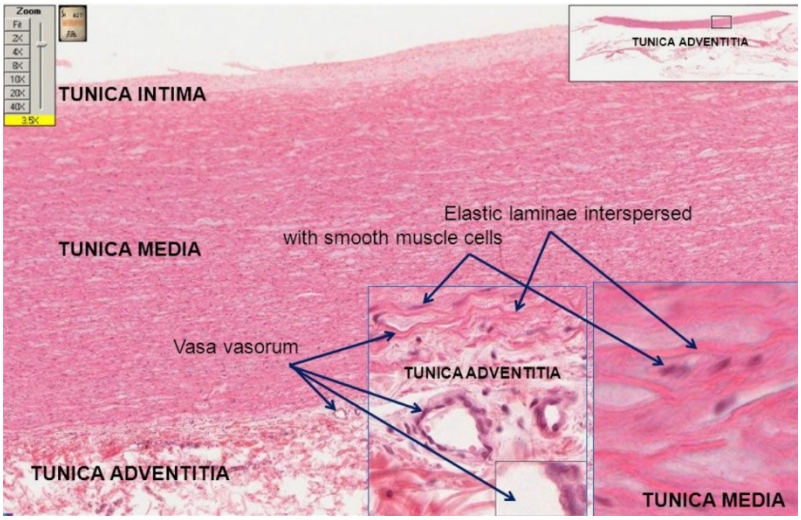

Figure 1- Histological layers of the aorta (from luminal to visceral side: tunica intima, tunica media and tunica adventitia). The infrarenal aorta has fewer elastic lamellae, collagen and vasa vasorum compared to other aortic compartments. Adapted from Johnson L. (1) Authorized reproduction.

1.1.3.2 Clinical Risk Factors in AAA Formation

Sex

Males, in general are at increased risk of developing an AAA. For instance, the prevalence of AAA in women aged 65 to 80 is up to six times lower than males of the same age (7).

Tobacco

Tobacco is the most important modifiable risk factor in AAA formation. It is estimated that up to 90% of all AAA patients have a history of tobacco use (32). The number of pack-years of smoking also increases the risk of finding an AAA on screening (4, 33).

Diabetes

A majority of studies have shown diabetes mellitus to be negatively associated with AAAs in the literature (4, 34-37). However, a minority of studies showed the contrary (34). Hypotheses include the action of metformin, which might be linked to AAA development prevention, or the reduction of matrix metalloproteinases (MMP) (38).

Vascular disease

Vascular disease might also be a risk factor for AAA development. Atherosclerosis is positively associated to AAA, as are culprits in atherosclerotic plaque formation such as hypertension and hyperlipidemia (39-41).

Family history

Family history is another risk factor for AAA development. It is estimated to increase AAA development risk by a factor of two compared to patients with no AAA family history (42, 43).

Ethnicity

Finally, older Caucasian males are at increased risk of developing AAAs (44, 45). Black, Hispanic and Asian males have also a lower risk of developing AAAs compared to Caucasian males (4).

1.1.3.3 AAA Pathogenesis

Immune Pathway

Transmural infiltration of inflammatory cells can occur in AAAs due to the various stressors that were exposed in the previous section. The most frequently encountered cells in these infiltrates are macrophages, B-cells and CD4+ T-cells (46-48). These cells convey a TH2 inflammatory response, resulting in heavy cytokine and antibody production (49). Two of these cytokines, namely Fas ligand and Fas-associated phosphatase-1 (FAP-1) engage in apoptosis of aortic wall smooth muscle cells, resulting in progressive weakening of the wall (49, 50). These inflammatory cells and smooth muscle cells engaged in apoptosis also secrete matrix metalloproteinases (MMPs) which destroy extracellular matrix, further damaging the aortic wall (47, 51). Another matrix damage pathway is the activation of the TH2 inflammatory response by reactive oxygen species (ROS) secretion by the inflammatory infiltrate, especially in smokers. These ROS also cause smooth muscle death and amplify the TH2 response (52, 53).

Atherosclerotic Pathway

Literature about the role of atherosclerosis in AAA development is controversial. In support of the atherosclerotic-related genesis of AAAs, most AAA patients have comorbidities involving atherosclerosis such as ischemic heart disease or peripheral artery disease. These diseases are known risk factors of AAA incidence (54). However, there is no clear evidence that atherosclerosis promotes AAA expansion, some reports even stating a link between atherosclerotic disease comorbidity and slower AAA growth (55-57).

1.1.3.4 Other Types of AAA Pathogenesis

Inflammatory AAA

Between 3 to 10% of all AAAs are thought to be inflammatory aneurysms. Inflammatory AAAs are defined by a triad of thickened aneurysmal wall, extensive perianeurysmal and retroperitoneal fibrosis, and dense adhesions to adjacent abdominal organs (58, 59). Other aneurysms have a traceable inflammatory cause such as giant cell arteritis. Giant cell arteritis, a systemic large and medium vessel inflammatory disease generally affecting those older than 50, can cause AAAs in rare cases (60, 61).

Infectious AAA

Infectious or mycotic abdominal aortic aneurysms are caused by bacteria infiltrating an intimal tear resulting in media destruction or vasa vasorum occlusion. These infiltrations thus weaken the aortic wall, which becomes prone to aneurysmal dilation. Infectious agents include staphylococcus aureus and salmonella. Patients are often immunocompromised or have concomitant infections, causing the death rate to be as high as 43% even with treatment (62, 63).

Connective tissue diseases

Connective tissue diseases can cause AAA in certain cases. For instance, Marfan syndrome is a genetic disorder in which the production of an essential component of connective tissue, fibrillin-1, is impaired (64). Most often, aneurysms appear at the root of the aorta but rarely do at the level of the infrarenal aorta (65, 66).

1.1.4 AAA Rupture

1.1.4.1 Clinical Risk Factors for AAA Rupture

AAA Maximal Diameter

AAA maximal diameter is the single most important and most validated predictor of rupture risk up to this day. Table 1 is a stratification of 12-month rupture risk based on various diameters. This data stems from the European Society for Vascular Surgery (67-70).

AAA Diameter (mm)	Rupture Risk (%)
30-39	0
40-49	1
50-59	1-11
60-69	10-22
>70	30-33

Table 1 - 12-month AAA rupture risk by diameter. The risk of AAA rupture increases with diameter, the steepest risk increment occurs at 50-59 mm.

Fast Expansion

An increase in size ≥5 mm over six months or ≥10 mm over 12 months is considered to be rapid expansion of an AAA (32). Maximal diameter growth accelerates as AAAs get larger, making them even more susceptible to rupture (56).

Tobacco

In addition to being associated with AAA development, tobacco is also a risk factor for AAA rupture (32, 71). Smoking cessation is the most effective nonsurgical intervention to reduce the risk of AAA rupture and death stemming from it (72).

Other Clinical Risk Factors for AAA Rupture

Data from the UK Small Aneurysm Trial, gathering information on 2257 patients, reveals hypertension, female sex and lower FEV1 to be culprits in increasing AAA rupture risk (73). Female sex is especially a strong predictor of rupture (73, 74).

Many studies have pointed at COPD (chronic obstructive pulmonary diseases) and a low FEV1 (forced expiratory volume in 1 second) to be independent AAA rupture risk factors (73, 75). This relation is preserved regardless of smoking status (73).

Heart and abdominal organ transplantation have also been linked to AAA rupture although it is presently unclear whether the increased risk is caused by the transplantation itself or by immunosuppressive drug administration following transplantation (76, 77).

Many observational studies associated fluoroquinolone use to an increased risk of AAA development or rupture (78-81). Namely, ciprofloxacin increases aortic elastin fragmentation and increases metalloproteinase production, which are known to contribute to AAA rupture. This conducted the FDA to emit a safety concern in 2018 to warn patients with increased AAA and AAA rupture risk to avoid fluoroquinolones (82).

1.1.4.2 Anatomical AAA Rupture Risk Factors

Wall Stress

Peak wall stress represents another possible interesting approach to predict AAA rupture (85). A 50-patient study where all participants were older than 40 years old and had AAAs with maximal diameters ≥ 40 mm showed that there was congruity between the heavily inflamed areas of an AAA with peak wall stress in only 16% of the cases. This led the investigators to conclude that, possibly, some aneurysms rupture due to high peak wall stress, whereas others rupture due to high inflammation (86). A recent French study found out that a regression model including lumen volume and wall shear stress to predict aneurysm enlargement was superior to maximal diameter alone, particularly in aneurysms smaller than 50 mm in diameter (83).

Intraluminal Thrombus (ILT)

Intraluminal thrombus has been poised by some observational studies as being a possible risk factor for AAA growth and rupture. These studies determined that, possibly, the larger the thrombus, the greater the rupture risk (84-86). A 2019 meta-analysis gathering eight studies for a total of 647 patients suggested that ILT volume is greater in patients with ruptured AAAs than in patients with intact AAAs, although this relation is most likely due to a larger diameter of ruptured AAAs as a confounder (87).

Calcifications

The implication of aortic wall calcification as a risk factor for AAA rupture remains controversial. A review of the literature on this subject can be found in section 1.2.

1.1.5 AAA Rupture Diagnosis

1.1.5.1 Clinical Diagnosis

History

Most commonly, AAAs are asymptomatic and are discovered incidentally while patients are investigated for an unrelated matter (88). Otherwise, if patients with AAAs are not picked up by any screening, they can possibly present with rupture (89).

AAA-related pain can be located in the abdomen, back, flanks, pelvis, or can radiate to the groin or to the thigh (90). A systematic review established the incidence of abdominal pain on presentation of a ruptured AAA to be between 49 and 72% (91).

Syncope can ensue from AAA rupture and can be a predictor of worse mortality outcome. A 73-patient American study found out syncope to be significantly correlated to higher mortality in multivariable analysis ($p<0.005$). Hypotension was also a significant risk factor for higher mortality as per the multivariable analysis in this study ($p<0.005$) (92).

AAAs might present with lower limb ischemia symptoms at first because of embolism of thrombus or atherosclerosis debris that detached from the aneurysm. If distal ischemia caused by embolism is associated to abdominal/back/flank/pelvic pain, this could be a sign of rupture (93, 94).

Physical Examination

The focused examination for an abdominal aortic aneurysm should be directed at the upper abdominal quadrants (32). Depending on abdominal girth and aneurysm size, an aneurysm might or might not be detectable on palpation. As physical exam is not very sensitive for this purpose, a negative physical exam should not prevent running other tests like imaging or labs (32).

A quick assessment of vital signs can be done at the beginning, with patients rupturing from the posterior aortic wall experiencing less severe hypotension than patients

rupturing from the anterior (90). Fever, as it was mentioned earlier, could be a sign of infectious aneurysm (95).

Retroperitoneal hematoma caused by AAA rupture can lead to blood extravasation in subcutaneous tissue. This process can cause ecchymosis at the flanks (Grey-Turner sign), around the umbilicus (Cullen's sign), at the proximal thigh (Fox's sign) and at the scrotum (Bryant's sign). These signs are unfortunately non-specific to AAA rupture as any retroperitoneal bleed can cause them such as pancreatitis, ectopic pregnancy rupture, etc (96).

The overall sensitivity of abdominal palpation for detecting AAA was estimated at 68% and the specificity at 75% (97). Palpation by itself does not precipitate rupture, and the concern for a symptomatic aneurysm should not prevent from performing a full examination (32).

1.1.5.2 Laboratory Testing

Consistently, fibrinogen, D-dimer, and interleukin 6 have been associated with the presence of AAA in case-control studies (98). A meta-analysis has reported that fibrinogen, D-dimer, and thrombin-antithrombin III complex levels are increased in patients with AAAs (99). Also, some microRNAs related to smooth muscle cell function and collagen formation have also been reported as possible AAA biomarkers (100-102). Currently, none of these biomarkers has the sensitivity, specificity, or rigorous clinical validation to rule-in or rule-out AAA presence or predict AAA rupture (103, 104).

1.1.5.3 Differential Diagnosis

The triad of back pain associated to abdominal pain, hypotension, and a pulsatile abdominal mass may only be present in 25% to 50% of AAA patients, making the diagnosis challenging. A retrospective study showed that ruptured AAAs were initially misdiagnosed as renal colic, perforated viscus, diverticulitis, gastrointestinal hemorrhage, or ischemic bowel in 30 % of 152 patients, based upon clinical symptoms

and signs alone (105). Therefore, AAAs and especially AAA rupture in patients with risk factors and comorbidities can prove to be tricky to diagnose. This is why these already sick patients with risk factors, with or without abdominal pain and/or positive physical exam benefit from urgent imaging (106).

1.1.5.3 Radiological Diagnosis

Decreased thrombus-to-patent lumen ratio

Decreased thrombus-to-patent lumen ratio caused by AAA increase in diameter, can be a sign of increased rupture risk (107). Pillari et al. indicated that decreasing thrombus volume with progressive enlargement of the true lumen could likely indicate lysis of the thrombus. New plaque erosion or eccentric outpouching of the lumen could therefore indicate instability in such setting (108, 109).

Hyperattenuating crescent sign

An utterly important sign in favor of impending rupture is the hyperattenuating crescent sign (107). The hyperattenuating crescent sign, which consists in a well-defined peripheral crescent of increased attenuation within the thrombus of a large AAA, is a CT sign of acute or impending rupture (2, 110, 111). This finding is best appreciated on unenhanced CT images (Figure 2). It is one of the earliest and most specific imaging manifestations of the rupture process (2, 110-112). Mehard et al. estimated the sensitivity and specificity of this sign in predicting risk of AAA rupture to be respectively 77% and 93% (111). Another study yielded a 95% specificity of the hyperattenuating crescent sign in predicting rupture (113).

These crescents have been linked to hemorrhages into the mural thrombus or into the aneurysmal wall, where blood from the lumen infiltrates cracks in the thrombus. The blood later reaches the aneurysm wall and weakens it (112, 114).

Focal discontinuity in calcifications

Finally, a focal discontinuity in circumferential wall calcifications is commonly observed in unstable or ruptured aneurysms (2, 115) (Figure 3).

Draped aorta sign

A draped aorta sign could support the diagnosis of impending aneurysmal rupture. This sign is present when the posterior part of the AAA drapes over the adjacent vertebrae and/or when there is no distinct border between the posterior aspect of the AAA and its adjacent structures (2, 107, 114, 116). Often, the draped aorta sign presents with loss of the normal fat plane (117). This sign may indicate aortic wall insufficiency and contained leak, even in the absence of retroperitoneal hemorrhage (114) (Figure 4).

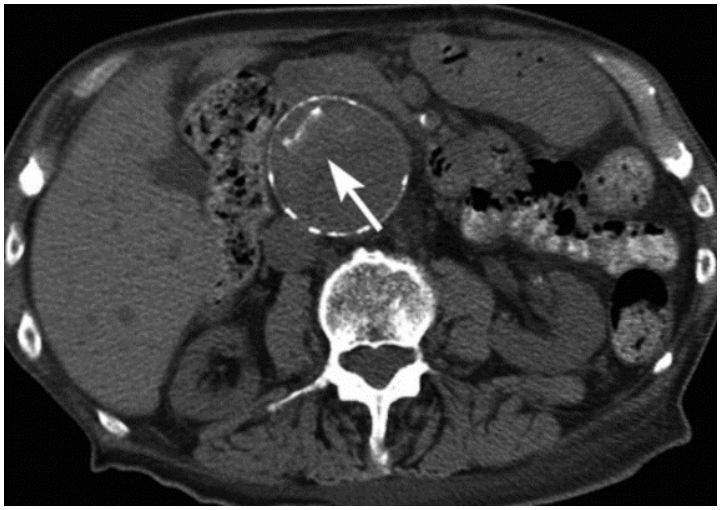

Figure 2 - Unenhanced axial CT showing a hyperattenuating crescent sign (white arrow). Adapted from Rakita et al. (2) Authorized reproduction.

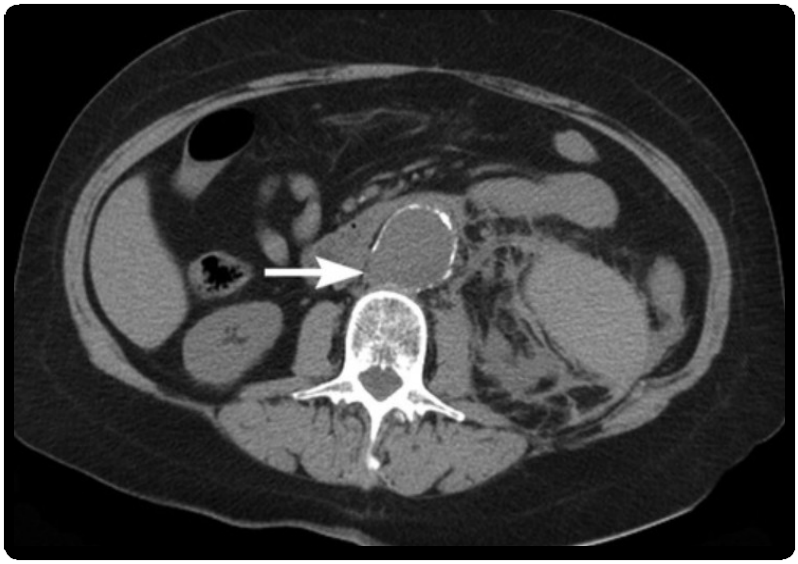

Figure 3 - Unenhanced axial CT showing discontinuity of aortic wall calcifications (white arrow)**.** Adapted from Rakita et al. (2) Authorized reproduction.

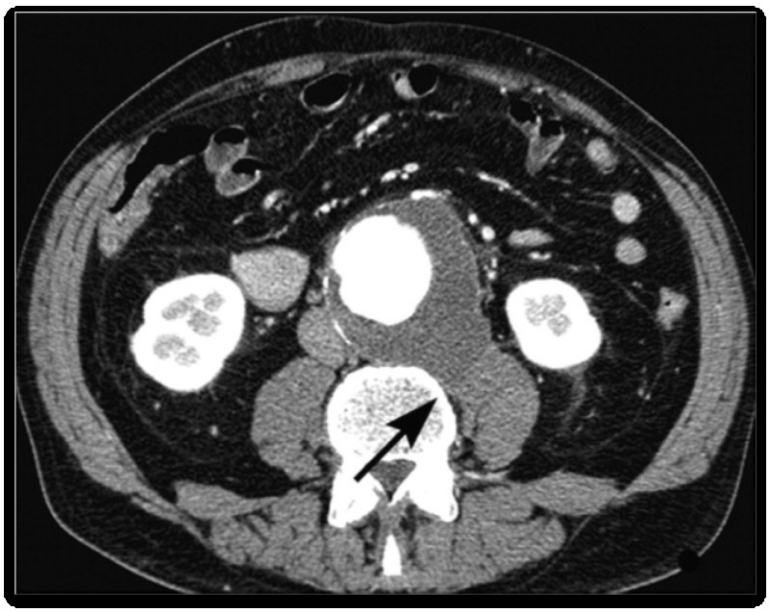

Figure 4 - Contrast-enhanced axial of an AAA with a draped aorta sign (black arrow). Adapted from Rakita et al. (2) Authorized reproduction.

Active extravasation of contrast

On contrast-enhanced CT, active extravasation of contrast is often observed in AAA rupture (2) (Figure 5). The posterolateral aspect of the aortic wall is the most common site of rupture in AAAs, which results in hemorrhage into the retroperitoneal spaces including the perirenal space, pararenal spaces, and psoas muscles (115). Intraperitoneal extravasation could also be noticed in AAA rupture, resulting from the disruption of the anterior or anterolateral aspect of the aneurysm (107).

Retroperitoneal hematoma

The classic AAA rupture triad, which includes abdominal pain, hypotension, and a pulsatile mass, is present in only 50% of rupture cases (117). However, a retroperitoneal hematoma adjacent to an abdominal aortic aneurysm is the most common imaging finding of AAA rupture (115). Periaortic blood may extend into the perirenal spaces, pararenal spaces, or into the psoas muscles. Intraperitoneal extension of blood could be an immediate or delayed finding (115) (Figure 6).

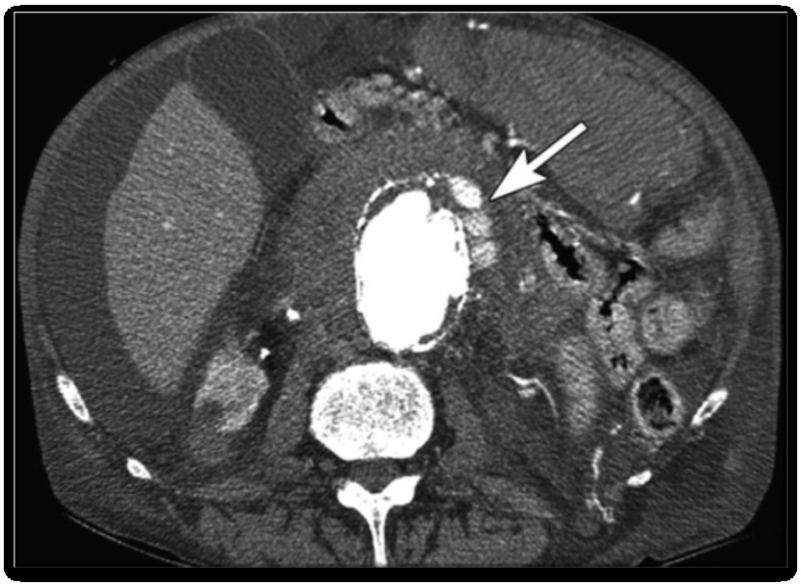

Figure 5 - Contrast-enhanced axial CT displaying contrast extravasation (arrow) in a ruptured AAA patient. Adapted from Rakita et al. (2) Authorized reproduction.

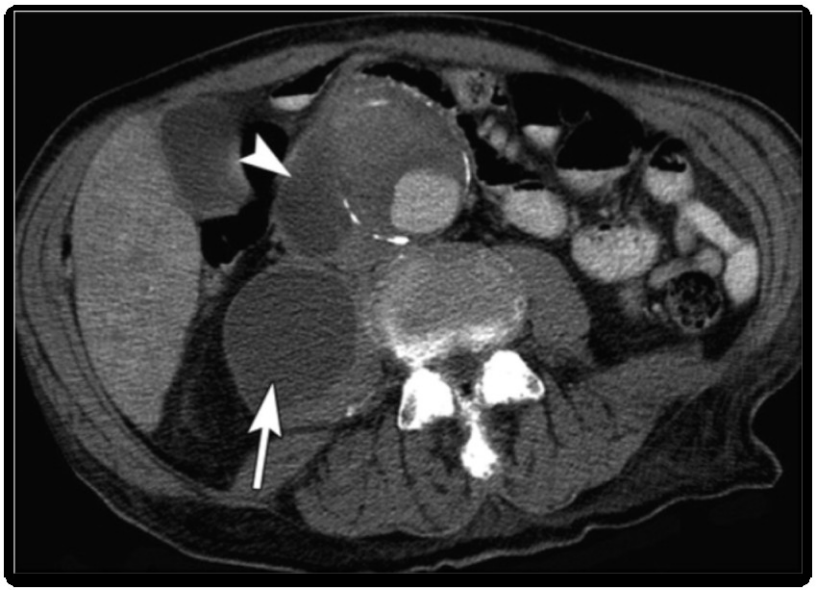

Figure 6 - Contrast-enhanced axial CT of a ruptured AAA. The image displays a retroperitoneal hematoma (arrowhead) and a right-psoas hematoma (arrow). Adapted from Rakita et al. (2) Authorized reproduction.

1.1.6 AAA Screening

US and Canada preventive healthcare task forces have advised for screening individuals at high risk of developing an AAA (118-120). The targeted population for screening is roughly the same in both countries, i.e. men older than 65 years old and younger than 75 or 80 years old depending on the country. Smoking is an additional criterion in the American screening guideline for someone to be considered for screening. These various recommendations have been summarized in Table 2. The modality for screening for both programs is ultrasound, which has a sensitivity ranging from 95 to 100% and a specificity of nearly 100% for AAA detection (32, 121-123).

	United States Preventive Services Task Forces (USPSTF) AAA Screening Program	**Canadian Task Force on Preventive Health (CTFPHC) AAA Screening Program**
Criteria	- Men aged 65 to 75 who have ever smoked - Men from 65 to 75 who have never smoked, but have significant past medical history, family history, AAA risk factors, and preference for screening	- Men aged 65 to 80
Modality	One-time ultrasonography	

Table 2 - North American AAA screening programs

Like with every screening policy, pros and cons must be weighed out. AAA screening programs have succeeded to decrease AAA-related mortality and rupture rates over time, but they come with many pitfalls, as this will be further reviewed in the next section.

1.1.6.1 Pros of Screening

Decrease in AAA-Related Mortality and AAA Rupture Incidence

A 2016 Canadian systematic review gathered data from four randomized controlled trials of moderate quality (124). All four trials were performed in various locations: two from the UK, the Multicenter Aneurysm Screening Study (MASS) (125-128) and the Chichester trial (7, 45, 129, 130), one from Denmark (44, 131-135), namely the Viborg trial and one from Western Australia (6, 136).

The systematic review encompassed more than 125,000 men aged 64 to 83. The investigators compared the effect of one-time ultrasonography AAA screening with no screening. The analysis showed significant reduction in AAA-related mortality and AAA rupture rate up to 13 to 15 years of follow-up with 42% reduction (risk ratio (RR), 0.58; 95% confidence interval (CI), 0.39-0.88; number needed to screen = 212) and 38% reduction (RR: 0.62; 95% CI, 0.45-0.86; number needed to screen = 200), respectively (124). It was later found that inviting only those men aged 65 to 74 years with a smoking history for a one-time screening would account for 89 % of the anticipated reduction in AAA-related mortality (137). Now that population screenings for AAA have been implemented in several countries, they have been shown to reduce AAA-related mortality by up to 50% (138).

Cost-Effectiveness

The MASS trial showed that over the initial four years, effectiveness of screening for abdominal aortic aneurysms was at the margin of acceptability according to current National Health Service (NHS) thresholds in terms of quality-adjusted life-year (QALY) cost. However, the investigators predicted the cost effectiveness to improve substantially over a 10-year period (139). Other subsequent studies came to the same conclusion. (126, 132). At the beginning of this chapter, it was mentioned that AAA epidemiology was changing over the last years. Despite this epidemiologic shift, cost effectiveness is maintained in statistical models (140-142).

1.1.6.2 Cons of Screening

Anxiety

Anxiety related to the discovery of a small aneurysm, which can lead to excessive anxiety in patients despite the minimal risk of rupture, can be an issue. Indeed, a Danish study showed that men found to have small AAAs had lower quality of life scores than controls. Even healthy men undergoing screening experienced a higher amount of stress compared to controls, until they found out they did not have any AAA (133).

Postoperative Complications

Subsequent AAA management also has some pitfalls. A retrospective cohort study encompassing around 40,000 Medicare patients showed the overall postoperative mortality was 1.6% with endovascular repair versus 5.2% with open repair ($P<0.001$) (19). EVAR has been estimated to have an incidence of endograft-related complications ranging from 16 to 30% (143, 144).

No benefit for women

The Chichester trial did not yield significant differences in AAA mortality (RR, 1.00; 95% CI, 0.37-2.65) and AAA rupture (RR, 1.11; 95% CI, 0.45-2.72) for up to 10 years of follow-up of women who had been screened versus non-screened women (7).

1.1.6.2 Summary of Screening

In summary, although screening programs have had an impact on decreasing AAA-related mortality and rupture rates, they face many challenges. These programs can engulf astronomical amounts of money making them only very thinly cost-effective. For women, the prevalence of AAAs is so small that most programs do not include them in their target screening population. Most AAAs that are discovered are small and can cause excessive unnecessary stress. Table 3 sums up the pros and cons of AAA screening. For all these reasons, we ought to find prognostic criteria to better manage discovered AAAs. This brings us to the next chapter.

Pros of AAA Screening	Cons of AAA Screening
- Decrease in AAA-related mortality and AAA rupture rate (124) - Cost effectiveness on the long run (126, 132) - Cost effectiveness maintained despite AAA epidemiological shift (140-142)	- Very high number needed to screen to avoid one death and one rupture (124) - No benefit in all-cause mortality (124) - Cost effectiveness very thin in first years of screening - No significant benefit for women - Psychological distress (133) and procedural risks (19, 145)

Table 3 - Pros and cons of AAA screening

1.1.7 AAA Management

This section summarizes the last recommendations of the Society for Vascular Surgery (SVS) in 2018 regarding the management of asymptomatic and symptomatic AAAs once they are discovered by screening or as an incidental finding (32). Essentially, for asymptomatic patients (Figure 7), AAA shape, diameter and patient sex determine the management, i.e. repair versus monitoring. Smoking cessation is, of course, advised for everybody. All patients with a saccular AAA need repair regardless of the diameter. For fusiform aneurysms, the management depends on AAA maximal diameter. All aneurysms with a maximal diameter inferior to 5.0 cm are watchfully monitored. For aneurysms with a maximal diameter ranging from 5.0 to 5.4 cm, sex determines management as all women in this range are required repair.

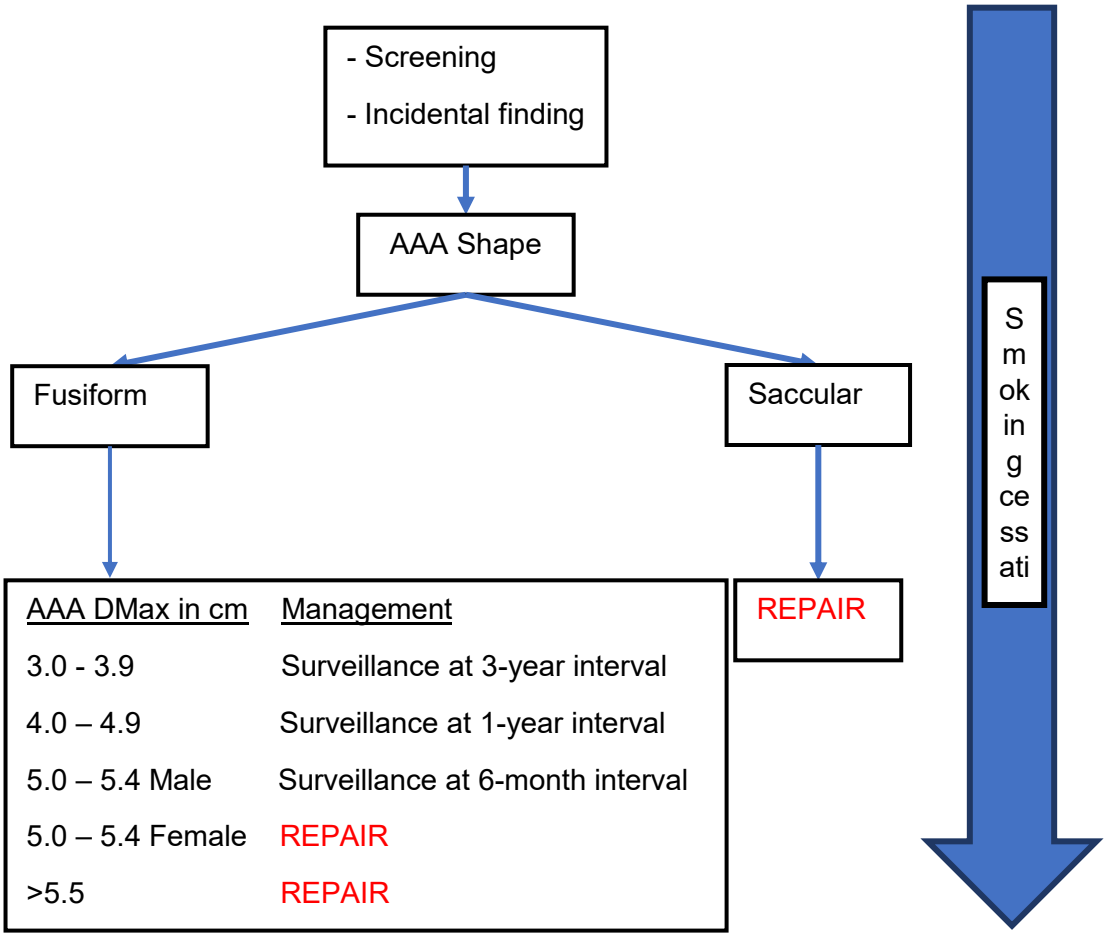

Figure 7- Management of asymptomatic AAAs as per 2018 SVS guidelines. Original work.

Also, the SVS suggests taking into consideration rapid growth of aneurysms (>5 mm in six months or 10 mm per year) on serial imaging studies performed by the same modality without formally emitting a recommendation (146-148). Otherwise, no pharmacological treatment has ever proven to be effective in reducing the occurrence of rupture or slowing aneurysmal growth during surveillance (149-152).

For asymptomatic patients, only aneurysmal diameter and sex determine access to repair. A 2012 case-control study established the sensitivity of these two parameters to be only 60% for a 77% specificity for rupture risk prediction (153). The study was conducted by Tang et al. at the CHUM and MUHC.

A retrospective study involving 24,000 autopsies found out that 40% of patients who had AAAs with 7 to 10 cm maximal diameters were not ruptured. On the other hand, 13% of aneurysms with maximal diameters <5 cm were ruptured (154). This data has led investigators to seek other factors associated with AAA rupture. Therefore, maximal diameter has its limits in AAA rupture prediction and more reliable biomarkers need to be discovered.

It is not currently possible to clearly tell a patient whether their aneurysm is likely to rupture based on their own morphology and not only on the general prevalence of rupture in patients who have similar diameters. This is why we need biomarkers that can yield a useful prognosis for AAA patients.

1.1.8 AAA Repair

Currently, 80% of aortic repairs are done endovascularly (EVAR) rather through open surgery (155). As of now, the UK National Institute for Health and Care Excellence (NICE) considers EVAR to provide more benefit than open surgery for most patients, especially men over 70 years old and women of any age (156). As per NICE, open surgery is likely to provide a better balance of benefits and harms in men under 70. These recommendations are based on a large body of research consisting in many randomized-controlled trials comparing EVAR and open surgery (157-163).

EVAR has been found to have less perioperative mortality than open surgery by trials like EVAR-1 or DREAM (157-161). The OVER trial found EVAR to be followed by shorter hospitalizations than open surgical repair (162, 163). However, these trials have also found EVAR to have higher rates of reintervention (5.1% in EVAR-1) and graft-related complications (12.6% in EVAR-1) (157-161). Complications of EVAR include graft rupture, infection or migration, organ ischemia, end leaks, i.e. blood seeping out of the endograft, ultimately leading to aneurysmal sac enlargement (157-161).

Also, EVAR patients are required to be followed-up extensively postoperatively. As per the SVS, all EVAR patients need CT and duplex ultrasound exams 1 month, 1 year and 5 years after the intervention. If patients suffer an endoleak, follow-up is required to be even more frequent (23, 32, 164). In addition to requiring cumbersome follow-up, EVAR is an expensive procedure. In the US, EVAR is estimated to cost up to $32,000, including perioperative care and hospitalization but excluding long-term follow-up costs (144). These considerations demonstrate that EVAR is not a benign procedure, therefore, only those patients who definitely need it should undergo this expensive, sometimes dangerous, intervention. For this reason, we need to improve the predictive value of the present-day rupture prediction model to only target those patients who have a very high likelihood of rupture. The pros and cons of EVAR are summarized in Table 5.

Pros of EVAR	Cons of EVAR
- Best suited for men over 70 years old and women of any age - Less perioperative mortality than open surgery - Esthetically more convenient for patients than open surgical repair - Shorter hospital stays than open surgical repair	- Not suited for all aortic anatomies - Significant postoperative complications (graft-related, need for reintervention, etc.) - Extensive postoperative follow-up - Elevated cost

Table 5. Pros and cons of Endovascular Aortic Repair (EVAR)

1.1.9 Abdominal Aortic Aneurysm Summary

Aneurysm rupture is difficult to predict and carries a significant morbidity and mortality. There are three main reasons justifying the need for new biomarkers that could better predict AAA rupture:

1. Although the prevalence of AAAs is decreasing over time, the population of Canada is aging, therefore there still is a possibility for an increase in AAA prevalence in the future.

2. Screening and follow-up based on sex and diameter has its limitations as it may lead to unnecessary anxiety and treatment. Studies have shown how are sex and maximal diameter poor at predicting individual rupture risk.

2. EVAR is not a benign intervention. EVAR requires significant follow-up, financial resources and can lead to important long-term complications. Therefore, we need to make sure the patients undergoing EVAR truly need it.

One of these possible biomarkers is aortic wall calcifications, which remains controversial in the literature. The next section of this document will attempt to summarize the current body of knowledge related to the putative role calcifications might play in AAA rupture.

1.2 AAA Wall Calcifications

1.2.1 Location of Calcifications within the Aortic Wall

Aortic wall calcifications can be divided in two distinct groups based on their location. Some of these calcifications are located on the intima, which is the surface in contact with the aortic lumen and blood flow. Another type of calcifications is found in the layer of connective tissue deeper to the intima, the media (165-168). For better visualization of all three layers of the aorta (intima, media, and adventitia) please refer to Fig 1. Table 11 compares intimal and medial calcification characteristics. On CT, it is not possible to differentiate between intimal and medial calcifications.

	Intimal Calcification	**Medial Calcification** (also called Monckenberg sclerosis)
Characteristics	- Associated with atherosclerosis - Frequent in abdominal aorta - Frequent in coronary arteries	- Not due to atherosclerosis - Especially in patients with renal failure and diabetes mellitus - Frequent in abdominal aorta - Rarely seen in coronary arteries

Table 4 - Comparison between intimal and medial calcifications in AAA

1.2.2 Clinical Factors Responsible for Calcification Growth

Some of the clinical factors responsible for AAA development are also involved in calcification development. These include age, male sex, diabetes mellitus, hypertension, renal failure, peripheral vascular disease and hyperlipidemia, the latter being controversial in the literature (169-178).

1.2.3 Calcification composition

Aortic wall calcifications do not have homogenous densities on CT scan. This is caused by a heterogenous composition of calcifications themselves. Depending on their density in Hounsfield units, these calcifications have different chemical compositions. Also, these calcifications, depending on their type, are embedded in fibers that differ in composition. This is better explained in Table 5 (3).

Tag on Fig.8	**Calcification Density**	**Macroscopic Phase of Calcification** (Chemical Composition in parentheses)	**Associated Fibers**
1	High	Nanocrystal (calcium hydroxyapatite)	Low collagen High elastin High myofilament
2	Medium	Amorphous material Nanocrystal Microcrystal (cholesterol hemimethanolate)	High collagen High elastin High myofilament
3	Low	Amorphous material Microcrystal	High collagen High elastin High myofilament

Table 5 - Calcification composition of aortic wall calcifications and their associated fibers.

Figure 8 represents a slice of calcified tissue from a human AAA under X-ray transmission microscopy (XTM). The dark and white image shows the absorption pattern of the slice, the darkest areas being the ones with higher densities. In this case, higher densities correspond to mainly calcium hydroxyapatite calcifications. The color image is a red green blue (RGB) map traced of the same slice with green for high, white for medium and purple for low absorption areas respectively. The red numbers represent different calcification density areas: 1 with high, 2 with medium and 3 with low density.

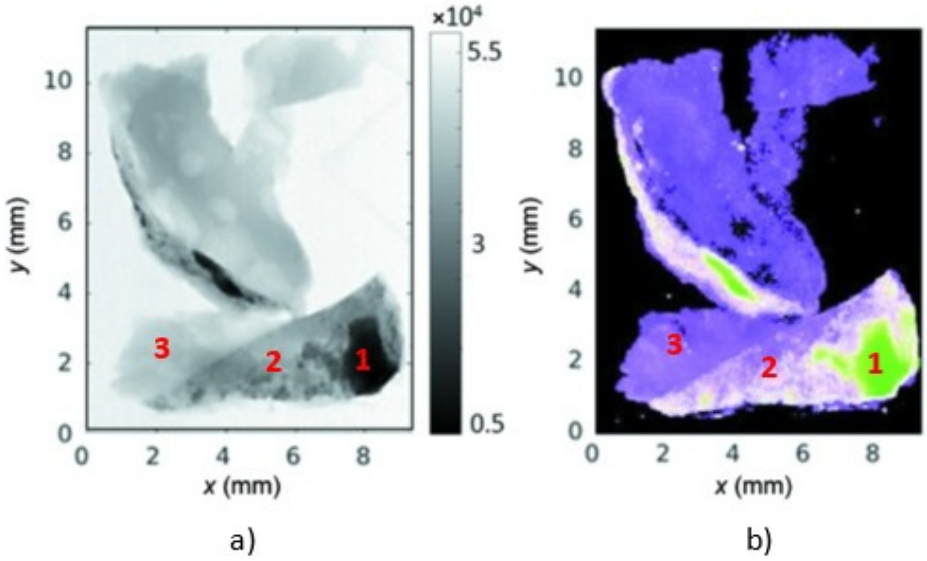

Figure 8 - X-ray density of an AAA calcified tissue sample. **8a)** X-ray transmission microscopy (XTM) image showing absorption patterns with the darkest regions being the most absorbing. **8b)** Red green blue (RGB) map traced on Fig. 8a), with green for high, white for medium and purple for low absorption areas respectively. High absorption correlates to high density. Adapted from Gianni et al. (3) Image free of rights.

1.2.4 Calcification Pathogenesis

Various processes in the human body can cause calcification growth. The macroscopic causes of calcification (ex: physiological stress, chronic diseases, metabolic process etc.) are still not well understood. However, there are many microscopic events that could result from these possible macroscopic stresses. For instance, chronic kidney disease (CKD) and henceforth chronic electrolyte abnormalities ensuing from inappropriate kidney function could trigger the production of certain transcription factors. These transcription factors like Runx-2, MSX2, Sox9 could transform vascular smooth muscle cells in osteochondrogenic-like cells, which in the end would produce calcifications (179). Other triggers of this pathway could be aging and diabetes (180, 181).

Another pathway through which CKD promotes vascular calcification buildup is through imbalances in promoters (hyperphosphatemia, hypercalcemia) versus inhibitors (Fetuin A, etc.) of calcifications (179). Otherwise, other mechanisms are at play in vascular calcification neogenesis. MicroRNAs have also been found to trigger that vascular smooth muscle cell change (182). Cell necrosis has also been shown to participate in vascular calcification buildup, although the main mechanism of calcification genesis is thought to be through vascular smooth muscle (cell mediated) (182, 183). Vascular calcification neogenesis is summarized in Figure 9.

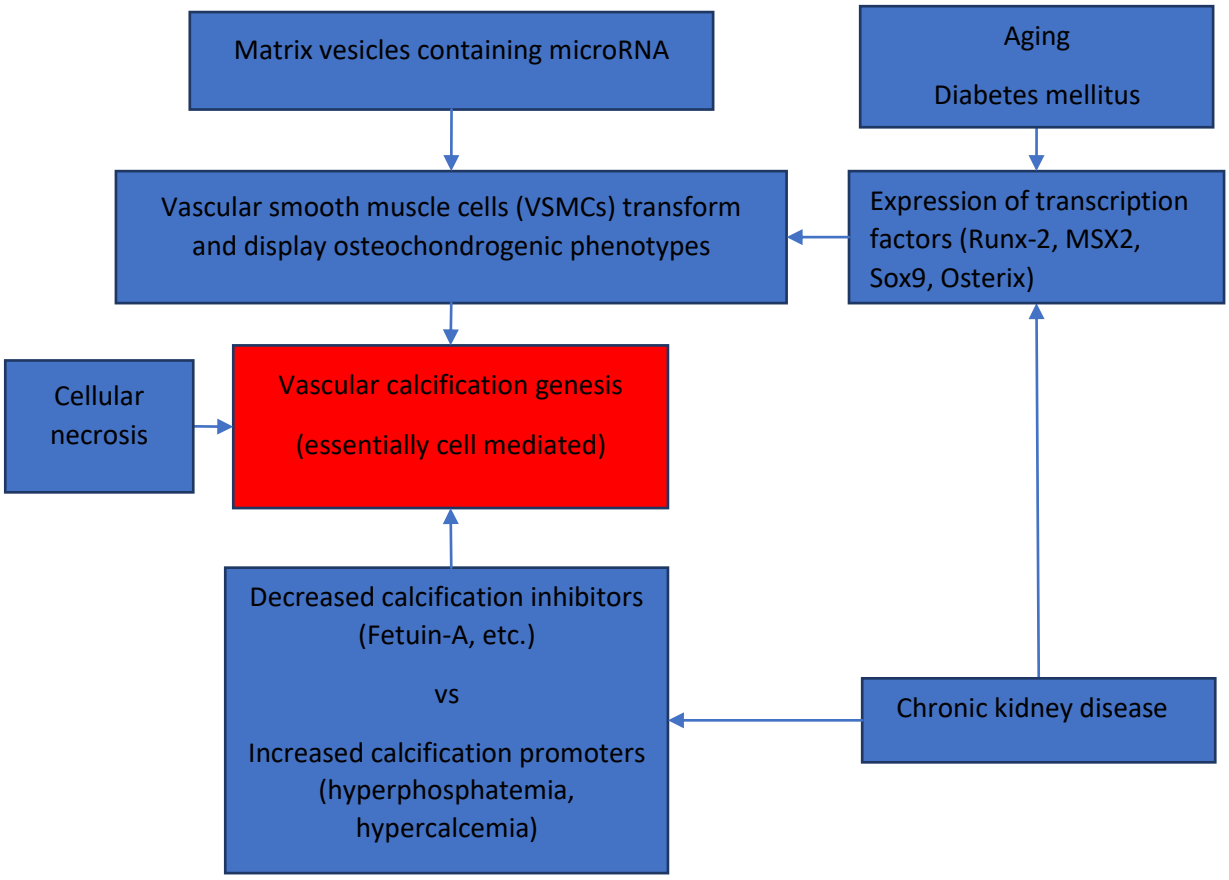

Figure 9 - Various mechanisms of vascular calcification pathogenesis. Original work.

1.2.5 Role of Aortic Wall Calcifications in AAA Rupture

1.2.5.1 Foundational Science Studies

Most AAAs exhibit localized calcifications in tunica media, which have been taken into account recently in AAA biomechanical modeling (184). There are conflicting reports on the role of calcifications in AAA rupture. Some reports support that calcifications increase AAA wall stress while others argue the contrary. Speelman et al. (185) and Li et al. (186) found that wall stress is increased by calcification whereas Maier et al. (187) found the contrary.

Computational Studies

Speelman et al. created a finite-element model from 6 AAA CT scans (185). They ran various simulations with and without calcifications to study the stress properties of AAAs. They isolated calcification by setting an empirical threshold of the mean aortic lumen blood intensity (in HU) plus four times the standard deviation of the lumen intensity and integrated the calcification as nodes in the finite-element analysis. To express the overall degree of calcifications for a given AAA via a single parameter, a calcification index (CI) was defined as the percentage of total wall surface area occupied by calcification (185).

They found that, in calcified sites, local stress significantly increased, leading to a maximum peak stress increment of 22% in the most severe case (185). They inferred that the inclusion of calcification in their finite element analysis of AAAs resulted in a marked alteration of stress distribution and should therefore be included in further rupture risk assessment. Furthermore, their results suggested that the location and shape of the calcified regions—not only the relative amount—were considerations that influenced AAA wall stress. For example, if areas predicted to have high stress even without calcifications do have minimally stiff calcifications located in them, the effect of these calcifications on wall stress will be pronounced (185).

A few limitations need to be discussed about this study. First, the material properties of non-aneurysmal calcifications were used in the simulations, which may be significantly different from aneurysmal calcification properties. Also, the authors acknowledged that they should have studied the effect of calcifications on the failing strength of AAAs in addition to wall stress. Another limitation was their implicit modeling of calcifications, which means they only changed the material properties of the underlying wall tissue to represent calcifications. They did not consider calcification as a separate and heterogenous constituent of the wall composite (185, 187).

Li et al. used a methodology similar to Speelman et al. by reconstructing 20 AAA models in 3D and then running a finite-element analysis on these to compute wall stress distribution (185, 186). This study assessed the influence of calcifications and intraluminal thrombus (ILT) on wall stress distribution. They considered 20 AAA contrast CTs on which they applied a Gaussian blur to reduce image noise and thus clarify the lumen boundaries. The lumen boundaries were then segmented automatically using a threshold based on intensity. The calcified regions were also picked up automatically during the threshold. The calcified areas were identified by subtracting the lumen region to the rest of the image. However, they did not specify the value of that HU intensity threshold. Their results showed a significant increase in AAA peak wall stress with the presence of calcification, suggesting that calcification decreases the biomechanical stability of AAA. Exclusion of calcifications from the analysis led to a significant decrease in maximum stress by a median of 14% (range: 2%-27%). They concluded that the presence of calcification increased AAA peak wall stress (186).

Maier et al. (187) reconstructed three AAAs and ran two simulations, one including all three AAA constituents (wall, ILT and calcifications) and one dismissing calcifications. Their results showed that calcification reduced average wall stress significantly in adjacent vessel wall by an average of 9.7 to 59.2%. For two out of three AAAs, peak wall stress decreased when taking calcifications into consideration (by 8.9 and 28.9%). For one AAA, simulated peak wall stress increased by 5.5%. They suggested neglecting contact to the spine in their simulation might have caused this peak wall stress

increment (187). Contrarily to Li et al. Maier et al. did not include small calcifications in their segmentation method (186, 187). Maier et al. argued that the most significant changes in peak wall stress were always found at positions with large underlying calcifications (187).

The contrasting results in computational studies such as Speelman et al. and Li et al. versus Maier et al. have been addressed by Raut et al. in a literature review (184). Speelman et al. modified the material property of the neighboring wall elements to represent stiffer calcium content (185). Maier et al. modeled calcification as being embedded in the ILT region, whereas Li et al. modeled calcifications embedded within the wall itself (186, 187). Raut et al. thus postulated that due to the relatively thin AAA wall, such subtle differences in the modeling approaches were likely to yield significantly different wall stress estimations. Also, Raut et al., mentioned a limitation of computational studies already formulated by Speelman et al.: material property models are scarce for aortic calcifications (184).

Another literature review published in 2018 summarized the extent of knowledge on the biomechanical effects of calcification as not being clear in general, and, in computational studies specifically, as being dependent on modelling assumptions (185-188). The two major biomechanical determinants for AAA rupture are wall stress and wall strength (185, 186). An AAA ruptures only when the local stress exceeds the local wall strength, therefore the best would be to test AAA tissue directly rather than running simulations based on AAA CT scans (186).

This leads us to a different type of studies that were designed to further understand AAA rupture: ex-vivo studies.

Ex-vivo Studies

Recently, Barrett et al. ran an experiment similar to O'Leary et al. (189, 190). They acquired 40 anterior ex-vivo AAA samples and 114 ILT samples on which stress testing and electron microscopy were performed. Under stress, tissue regions surrounding calcification, peak strains increased by a mean of 174% and corresponding peak stresses by 18.2% as a result of calcifications. For definition purposes, stress is the amount of force applied to a cross-sectional area whereas strain is the amount of deformation caused by stress in the direction of the applied force divided by the initial length of the material. Barrett et al. postulated that the mismatch in compliance between stiff calcium depositions and distensible wall causes an increase in strain in the surrounding wall tissue, thereby increasing AAA rupture risk. Limitations of the study included only taking samples from anterior AAA walls and like most of the computational studies presented in this review, there was no control group to have an estimate of the influence of calcifications in non-aneurysmal aortas (190).

In 2015, O'Leary et al. performed mechanical tensile failure tests on AAA samples harvested from 31 patients undergoing open AAA surgical repair (189). The samples were divided in two groups, one consisting of fibrous tissue (n=31) and one of partially calcified tissue (n=38). The presence of calcifications was confirmed by infrared spectroscopy. The samples had been subjected to failure stress (another term for strength), failure stretch and failure tension tests. Following mechanical testing, failure sites of a subset of both fibrous and partially calcified tissue were examined under electron microscopy and X-ray spectroscopy to investigate the potential reasons for failure. They concluded that the failure properties of partially calcified tissue were significantly reduced, compared to fibrous tissue. The junction between a calcification deposit and the fibrous matrix was highly susceptible to failure, suggesting possible calcification implication in rupture (189). Limitations of the study included only taking anterior AAA samples, not having full AAA samples to inflate them and no quantification of calcium load on the samples (189).

1.2.5.2 Clinical Studies

After having gone through the fundamental biomechanical evidence regarding the effect of calcifications on AAA rupture, we will review a few clinical studies that attempted to tackle this complex issue.

PET-CT Studies

Recently a new ledge emerged in the field of aortic aneurysmal calcifications. Fluorine-18-sodium fluoride (18F-NaF) PET-CT, became a hot topic as a potential predictor of AAA growth and/or rupture. Indeed, 18F-NaF uptake is a marker of active vascular calcification formation, which makes it a great tool to study their formation and effect on AAA growth or rupture (191).

A recent study using 18F-NaF micro-PET-CT found out that 18F-NaF uptake was significantly increased in AAAs compared to non-aneurysmal regions of the same aorta ($p = 0.004$) and aortas of control subjects ($p = 0.023$). (191). Aneurysms in the highest tertile of 18F-NaF uptake expanded 2.5 times more rapidly than those in the lowest tertile (3.10 [interquartile range (IQR): 2.34 to 5.92 mm/year] vs. 1.24 [IQR: 0.52 to 2.92 mm/year]; $p = 0.008$) and were almost 3 times as likely to require AAA repair or suffer rupture (15.3% vs. 5.6%; log-rank $p = 0.043$). The authors specified that this study was first and foremost a proof-of-concept and that the small number of rupture events made adjustment for confounders and covariates challenging (191).

There is also literature on cardiovascular calcifications suggesting that calcifications could cause inflammation to surrounding tissues (192). For instance, New et al. described biochemical analyses of calcified coronary arteries and stated that micro-calcifications can lead to inflammatory cytokine production, while macro-calcification plaques tend to be more stable and less pro-inflammatory (192, 193). Dweck et al. performed a functional analysis of coronary arteries with 18F-sodium fluoride positron emission tomography–CT and noted a significant rise in cardiovascular risk with micro-calcifications (192, 194).

Observational Studies

In Lindholt et al., 122 men with small AAAs ranging from 30 to 49 mm were selected. They were divided in two groups depending on whether AAA calcification was more or less than 50% of the initial maximal AAA circumference (195). The authors found significantly slower expansion rates of AAAs in men with AAAs containing calcifications in more than 50% of the total AAA wall circumference. Despite these findings, mortality was similar in both groups. AAA-related hospital admissions were significantly lower in >50% calcified AAAs in the univariate analysis. The authors concluded that as per their results, although calcifications were not protective against AAA-related mortality or hospitalization, it might be protective against aneurysm expansion (195, 196).

In a Dutch case–control study, Buijs et al. matched 91 non-electively treated AAA patients deemed as "non-eAAA" (because of AAA-related symptoms or rupture) with 233 electively-treated AAA patients (eAAA). The Abdominal Aortic Calcification-8 score (AAC-8) was used to measure the severity of aortic calcification. To perform this technique, the anterior and posterior aortic walls were divided into four segments (8 segments in total) on a maximum intensity projection volume, corresponding to the areas in front of lumbar vertebrae L1–L4. Within each of these 8 segments, aortic calcifications were recognized visually as either a discrete line consisting of many white dots or as white linear calcification of the anterior and/or posterior aortic walls. A score of zero was given if there was no calcification, a score of 1 if one third or less of the aortic wall in that segment was calcified, as 2 if more than one third but two thirds or less of the aortic wall was calcified, or as 3 if more than two thirds of the aortic wall was calcified. Therefore, scores could range from 0 to 6 for each vertebral level, and the total score range would be from 0 to 24 (197, 198). This score was used because it is able to detect calcification in contrast CT, given all preoperative AAA assessment is done with contrast in the Netherlands (192, 199, 200). Regression analysis with age and sex matching demonstrated an overall significant odds ratio of 1.34 increase of symptomatic AAA/rupture risk per point increase in AAC-8 score ($p<0.001$). The major limitation of the study was the AAC-8 score itself, which the authors acknowledged to be highly

observer dependent. Additionally, the AAC-8 score could not distinguish between micro- and macro-calcification (192).

A Japanese team, Nakayama et al. gathered data on 414 patients with AAAs who had undergone at least two sequential non-contrast CT scans with a minimum of 90 days between them. 344 patients had undergone AAA repair (314 elective repairs; 30 emergency repairs), and 70 patients had not. Calcifications were segmented using a 130-HU threshold on a manually plotted region of interest (ROI). The calcified area divided by the total area of the ROI was taken as the %calcification index of that slice. Finally, the average of the %calcification index of all slices of an AAA was defined as the %calcification index of that AAA (201).

Regression analysis showed that AAA expansion, which was converted from the increase in AAA maximal diameter between the initial and follow-up CT to an annual rate (mm/year), was significantly inversely correlated with the calcification index of the AAA measured at initial CT. Significance of this relation was not altered by the removal of extreme expansion rates or the removal of patients with hemodialysis. Receiver operating characteristic (ROC) curve analysis was performed to predict accelerated AAA expansion superior to 5 mm per year. The best cut-off for a %calcification index of AAA was <2.74% (sensitivity 82.1%; specificity 57.1%) A multivariate analysis found various significant odds ratios for an accelerated AAA expansion rate of >5 mm/year: creatinine >132 µmol/L (OR: 3.39), AAA diameter > 45 mm (OR: 2.27) and most importantly %calcification index of AAA < 2.74% (OR: 6.14) (201).

A notable limitation of the study was that all subjects were of Japanese ethnicity and came from the same hospital. Another limitation was the impossibility for the authors to distinguish between mural calcification and calcification found in the intraluminal thrombus. They also pinpointed that the location of calcifications (whether it is located on the site of maximum wall stress or not) might be more of a key than considering the overall calcification load (201).

1.2.5.3 Role of Aortic Wall Calcifications in AAA Rupture Summary

Through these studies, we can see that the subject of calcification involvement in AAA rupture is still controversial in the literature. To this day, there has been a lot of basic science papers involving fine-element analyses and/or ex-vivo tensile tests. There have been very few clinical studies, which, by the way, do not agree on the role of calcifications in AAA rupture (Table 6).

Types of study		**Calcifications Deleterious for AAA Stability**	**Calcifications as Promoters of AAA Stability**
Basic Science Studies	**Computational Studies**	Speelman et al. Li et al.	Maier et al.
	Ex-vivo AAA Sample Studies	Barrett et al. O'Leary et al.	
Clinical Studies	**PET-CT Studies**	Dweck et al. Forsythe et al.	
	Observational Studies	Buijs et al.	Lindholt et al. Nakayama et al.

Table 6 - Conflicting studies on the role of calcifications in AAA stability

Now that we presented the potential role of aortic wall calcifications in being a new biomarker to better predict AAA rupture risk, we need to review the different ways to isolate calcifications on CT scan images.

1.2.6 CT Scan Calcification Scoring Methods

Calcifications on a CT scan can be isolated automatically by instructing dedicated software to discard all pixels that have a lower density than a set HU threshold. Table 10 shows multiple HU densities depending on the structure. The red line represents an HU threshold of 130HU. In that case, all the densities below (air, fat, water, blood and some IV contrast) are discarded from the CT image (202).

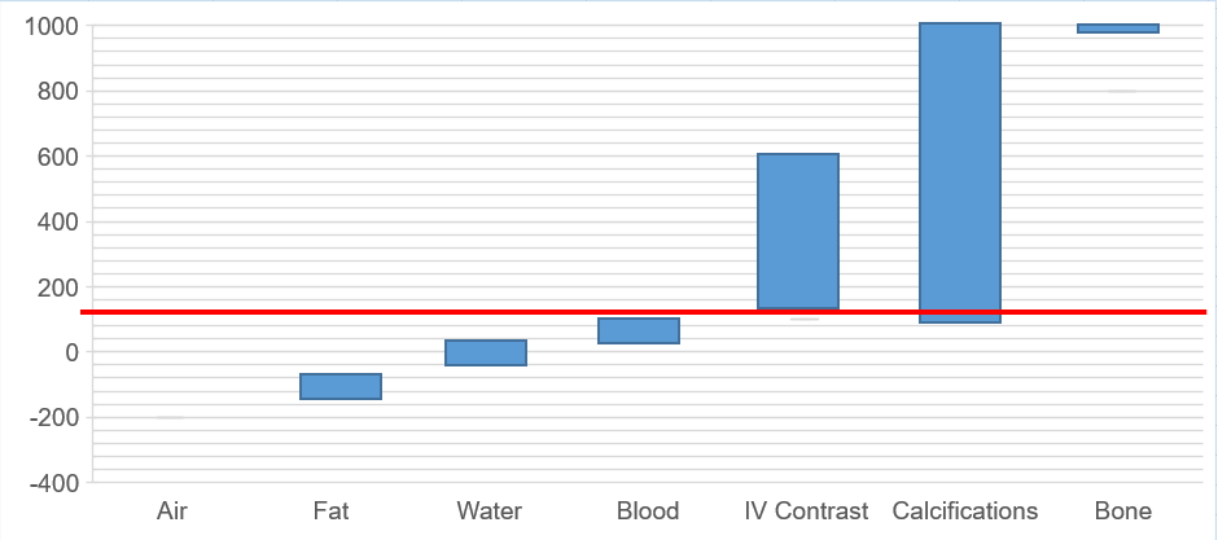

Figure 10 - Multiple HU densities depending on the structure. The red line represents a threshold of 130HU. Air <-1000 HU, Fat -70 to -30 HU, Water -20 to 20 HU, Blood 60 to 100 HU, IV contrast 100 to 600 HU, Calcifications 130 to 1000 HU, Bone >1000 HU. Original work.

There are multiple ways to isolate calcifications on CT scan. The most commonly used is the Agatston method, especially for coronary artery calcifications. The Agatston score is explained in detail in Table 7. This isolation method cannot be used with contrast-enhanced CT scans given the 130HU threshold it uses is lower than IV contrast (typically 100-600HU). Therefore, it is not possible to sort out calcifications from surrounding IV contrast with this scoring technique (192, 199, 203).

Another method is the Abdominal Aortic Calcification-8 score (AAC-8) which has been used by Buijs et al. in their 2013 case-control study (192). This score can be used with contrast-enhanced scans but is very observer dependent (197, 198, 204) (Table 8).

The 500-HU threshold method is the only method suitable for C+ CT scans with no observer dependence. The biggest drawback of this method is calcification erosion caused by the high threshold (Table 9) (205, 206).

Speelman et al. isolated calcifications by setting an empirical threshold = average aortic lumen density + 4 x standard deviation aortic lumen density. This method would in theory work with C+ scans but in a dataset of patients with very heterogenous contrast densities, the standard deviation would be too high. Following this method, the calculated threshold would be so high it would prune most calcifications (Table 10) (185, 186).

Agatston Score	
Scoring principle	- Lower threshold set at 130 HU. A given area would light up only if density in HU (Hounsfield Units) ≥ 130 and area ≥ 1 mm^2 to eliminate noise (199) - A lesion score would be determined based on the maximal HU value in a given area: a score of 1 if the maximal HU value would range from 130 HU to 199 HU , 2 from 200 to 299 HU, 3 from 300 HU to 399 HU, and 4 above 400 HU -After that, a score for each region of interest would be calculated by multiplying the density score and the surface area. The scores from all slices would be added up to yield a total score
Pros	-Quantifiable - Agatston score remains the gold standard for coronary calcifications -Reference score tables available for different populations (age /sex/ethnicity)
Cons	- Can only interpret calcifications in non-contrast CT images (192) - Only yields surface calcification values, but no volume (199) - Score entirely based on a single pixel within each lesion (i.e. in 2 similar lesions, one with 10 pixels of 199 HU density and a second lesion with 9 pixels of 199 HU and 1 pixel of 200 HU, the second lesion will double the score of the first lesion because the sole 200 HU pixel will take the whole lesion to an upper bracket (2 points in 200 to 299 HU bracket) (207)

Table 7 - Agatston score principle, pros and cons

AAC-8 score	
Scoring Principle	- Abdominal Aortic Calcification-8 score (AAC-8) used to measure the severity of aortic calcification - A volume maximum intensity projection is created. Anterior and posterior aortic walls are divided into four segments (8 segments in total) corresponding to the areas in front of the lumbar vertebrae L1–L4. Within each of these 8 segments, aortic calcifications are recognized visually as either a discrete line consisting of many white dots or as white linear calcification of the anterior and/or posterior aortic walls. Aortic calcification is scored as zero if there is no calcification, as 1 if 1/3 or less of the aortic wall in that segment is calcified, as 2 if more than 1/3 but 2/3 or less of the aortic wall is calcified, or as 3 if more than 2/3 of the aortic wall is calcified. Therefore, scores could range from 0 to 6 for each vertebral level, and the total score range was from 0 to 24.
Pros	- Can interpret calcifications in contrast CT images. - Only score that is specific to aortic calcifications and not to coronary vessels
Cons	-Not suited to reliably differentiate between micro and macro calcification -Cannot determine volume of calcification nor surface of calcification -Very observer dependent

Table 8 - AAC-8 score principle, pros and cons

500-HU Threshold Score	
Scoring principle	- First used in contrast-enhanced CT scan internal carotid artery calcification segmentation (205) - Lower threshold set at 500 HU to eliminate intravascular contrast and try to isolate calcifications as much as possible (205) - Also used by Komen et al. to segment iliac arteries in contrast-enhanced CT pelvic scans (206)
Pros	- Quantifiable (yields surface and volume) - Can isolate calcifications even in C+ CT scans. - Not observer-dependent - Can yield volume and surface of calcifications
Cons	- Calcification erosion (only picks up most dense parts of a calcification, which makes it appear smaller post segmentation)

Table 9 - 500-HU threshold score principle, pros and cons

Empirical Threshold Score	
Scoring principle	- Used by Speelman et al (185, 186) - Empirical threshold = average aortic lumen density + 4 x standard deviation of aortic lumen density.
Pros	- Quantifiable (yields surface and volume) - Can isolate calcifications even in C+ CT scans. - Not observer-dependent - Adaptable to different IV contrast phases - Minimizes calcification erosion
Cons	- Requires standardized IV contrast injection through patient body to avoid high standard deviation and result in a threshold that would erode most calcifications.

Table 10- Empirical threshold scoring principle, pros and cons

Section 2- Article

CT Machine Learning Analysis of Calcifications to Predict Abdominal Aortic Aneurysm Rupture

Original article

Key words: CT scan, Calcifications, Abdominal Aortic Aneurysm, Rupture, Machine Learning

Abbreviations:

AAA: Abdominal aortic aneurysm

AUC: Area under the curve

C+: Contrast-enhanced CT Scan

C-: Unenhanced CT Scan

CHUM: Centre Hospitalier de l'Université de Montréal

Dmax: maximal diameter

EVAR: Endovascular aortic repair

HU: Hounsfield Units

MUHC: McGill University Hospital Center

ROC: Receiving-operating characteristic

Key Points:

1. For a given calcification volume, AAAs with a larger number of well-distributed calcification clusters are less likely to rupture.

2. A model including AAA calcifications better predicts rupture compared to a model based solely on DMax and sex alone.

Summary statement: **Ruptured aneurysms are more likely to have their calcification load concentrated in a small number of clusters which are closer to each other which makes rupture prediction more sensitive.**

Introduction

In the United States, the prevalence of abdominal aortic aneurysms (AAA) is estimated at 1.4% in those aged between 50 and 84 which corresponds to 1.1 million people (208). Although it is most often an asymptomatic condition, the lethality of ruptured AAAs still ranges between 80 and 95% (209). The main predictor of AAA rupture is the maximal diameter (DMax) of the AAA (210). Other risk factors for rupture include the expansion rate of the aneurysm, a recent surgery, uncontrolled hypertension and smoking (211). However, the predictive model based on maximum diameter and sex only yields a 60% sensitivity and 77% specificity (AUC 0.67) for rupture risk prediction (153).

Other potential risk factors for rupture have been studied, such as blood biomarkers or aortic stiffness but none of them showed sufficient accuracy to be linked to rupture (212-216). Hence, this poor ability to predict rupture results in many patients having to undergo EVAR, a fairly morbid and expensive intervention, while many of these patients would have never ruptured if left untreated. 80% of aortic repairs are done with EVAR and this procedure is estimated to have an incidence of endograft-related complications ranging from 16 to 30% (143, 144). EVAR in the United States is estimated to cost up to $32,000 (144). Therefore, new predictive parameters are needed to increase the sensitivity, specificity, and overall accuracy of AAA rupture prediction.

Various computational and clinical studies have raised calcifications as a possible factor contributing to the rupture of AAAs (185, 186, 189, 190, 192)

while others have inferred the contrary (187, 195, 201, 217). Only a few clinical studies examined the link between aortic calcifications and AAA rupture through different scores and modalities, although never with semi-automatically quantified calcifications on C+ CT scans (192, 195, 201). This point is even more crucial given C+ CT scan is the primary modality to evaluate AAA morphology and eligibility to endovascular repair (192).

Our hypothesis was that the calcification load and distribution within the AAA wall could improve rupture prediction. The goal of this project was to assess whether aortic calcification load and distribution on CT might be able to predict AAA rupture through a machine learning analysis.

Materials and Methods

This retrospective study received approval from the institutional review board of both participating centers and written informed consent was waived. There were no conflicts of interest. Eleven of the patients included in this study were previously included in a previous study (153).This previous study assessed the impact of various AAA geometrical indices on AAA rupture whereas this study investigated the impact of AAA wall calcifications on rupture.

Patients

Medical archives were screened over a period of 17 years (between January 2001 and August 2018) for ruptured and non-ruptured AAA repair billing codes. Subsequently, CHUM RIS-PACS and MUHC ODIN imaging databases were cross-matched with the medical archives list to find patients with available CT scans images. The terms used in the imaging search are presented in appendix 1 of this article. OACIS electronic medical record system from CHUM and MUHC were consulted for demographic and clinical data.

After the application of inclusion and exclusion criteria, we ended up with 80 patients who had been diagnosed with a ruptured AAA on CT scan report or surgical report. These patients were matched to 80 patients who had been treated electively for a non-ruptured AAA during the same period (between January 2001 and August 2018). The inclusion and exclusion criteria and patient flow chart are detailed in Figure 1. To be included in the study, patients with a ruptured and non-ruptured AAA had to have a diagnosis of ruptured AAA/ non-

ruptured AAA and an abdominal CT scan done <1y prior to rupture/elective repair. The diagnosis of ruptured or non-ruptured AAA was made on CT scan report. If the CT scan report was unavailable, the surgical report would be consulted. CT scan slice thickness had to be limited to a maximum of 2 mm as any thickness above that could not be properly segmented.

Matching

Patients with ruptured AAAs were matched to a 1:1 ratio with patients with non-ruptured AAAs based on DMax (non-ruptured AAA diameter within +/- 10% of the ruptured AAA maximal diameter), sex, age (age of patient with non-ruptured AAA within +/- 12 years of age of patient with ruptured AAA) and use of contrast agent. Matching was done on a trial and error basis. We screened 420 non-ruptured patients from CHUM and 803 from MUHC to gather our patient list. Matching was done to have a reliable univariable analysis devoid of potential confounders, especially given we did not compute any regression analysis.

Calcification segmentation

Given the retrospective design of the study, multiple CT scan acquisition protocols were used. The majority (79%) of CT scans were C+ while 21% were C-. HU density threshold for calcification segmentation was set at 500 (205, 206).

AAAs were segmented from the lowest renal artery insertion into the aorta (excluding any accessory renal arteries) to the iliac bifurcation. Calcification segmentation was semi-automatically performed on ITK-Snap (Version 3.6.0, University of Pennsylvania, Philadelphia, PA, open source) by medical students

(MM, OZ, AR, MF) while AAA wall segmentation was semi-automatically performed on ORS (Version 1.5.1, Object Research Systems, Montreal, Canada, commercially available) by MM and OZ (Figure 2). Two radiologists with 25 years of experience (GS and ET) reviewed the most anatomically challenging AAA wall and calcification segmentations.

The proximal neck was set as being a non-dilated cylinder beginning proximally at the juxtarenal area and extending to the first CT scan slice showing a diameter equating to 1.15 x juxtarenal diameter (218). If the aorta was aneurysmal (i.e. aortic diameter > 3cm) in the juxtarenal region, it was deemed as having no neck. Calcification volume, number and surface as well as dispersion expressed as Euler distance were computed on Matlab (Version 9.5, Mathworks, Natick, MA, commercially available).

Machine Learning Analysis

Univariable analysis was performed with the Student t test for continuous variables (demographic, clinical and radiological) and with Pearson's X^2 for discontinuous variables on Excel (Version 2019, Microsoft, Redmond, WA, commercially available). All tests were two-sided with a significance value of $P<0.05$.

Prior to the machine learning analysis we removed 28 patients from the initial dataset of 160 patients (21 ruptured and 7 non-ruptured) because of missing clinical data. We removed two variables (total calcification volume and surface) that were correlated with an $R^2>0.95$ to other variables in the dataset. We ended

up with a table of 132 patients x 17 variables. ExtraTrees Classfier was first used to compute this table, from which we took the five best variables after classification. The variables that were drawn out were those that had the most important impact on classification by the machine-learning algorithm. Using 5-fold cross validation, the five variables were then recomputed with XGBoost. All operations on the dataset were performed using the Scikit-learn package on Python (Version 3.9.6, Python Software Foundation, Wilmington, DE, open source) (219). In order to refine models hyperparameters, we performed a grid search on the XGBoost models number of learners from 10 to 210, by steps of 20, and their associated depth, from 3 to 11.

It was not possible to compute a classifier strictly based on sex and DMax given we matched patients for these parameters. Therefore, we compared our model with a sex and diameter model built in Tang et al., a similar study to ours population-wise carried at the same centers from which we have also included 11 patients as it was mentioned above (153).

Results

From all initial 211 patients with a ruptured AAA on CT/OR report and a CT scan <1 year prior to rupture, 57 were excluded for not meeting radiological criteria, 56 for clinical criteria and 18 for segmentation criteria (Figure 1). The remaining 80 patients with a ruptured AAA were subsequently matched to 80 patients with electively treated non-ruptured AAA, for a total of 160 patients in the cohort, with a mean age of 74.0 ± 8.4 years, 142 of which were men (89%). Those patients with ruptured AAAs having had a CT scan on the same day as rupture accounted for 76% (61/80) of cases. A total of 6% (5/80) of patients in the non-ruptured group had a CT scan the same day as repair (Table 1).

Age at index date (rupture date versus repair date for non-ruptured patients) was not different between both ruptured and non-ruptured groups (73.9 ± 8.3 vs 74.2 ± 8.6, p= 0.826). Patients with a ruptured AAA had their CT scan done significantly closer to index date than non-ruptured AAA patients (8.1 ± 27.1 days versus 48.5 ± 69.1 days, p<0.00001). There was no difference in terms of comorbidities between both groups, except for a greater proportion of patients treated with beta-blockers (41% versus 59%, p=0.037), antiplatelet (53% vs 80%, p=0.001) and lipid-lowering drugs (53% vs 75%, p=0.006) in the non-ruptured group (Table 1).

In the univariable analysis, ruptured aneurysms were less likely to have a proximal neck than the non-ruptured (45.0% vs 76%, p<0.0001). Maximal diameter of aneurysms was not significantly different between both groups (80.8

± 17.6 vs 79.0 ± 17.3 mm, p= 0.505). Ruptured aneurysms contained a significantly smaller number of calcification chunks than the non-ruptured (18.0 ± 17.9 vs 25.6 ± 18.9, p=0.010) (Table 2).

Rupture status prediction using ExtraTrees classifier on all initial variables yielded an AUC of 0.61±0.08 (Figure 3 a)). Using ExtraTrees Classifier on the initial dataset, the five most important variables that came out of the classification were namely: neck presence, antiplatelet use, aneurysmal calcification number, Euler distance between calcifications mean value, and Euler distance between calcifications standard deviation (Figure 3 b)). Rupture status prediction using XGBoost classifier on all initial variables yielded an AUC of 0.81±0.04, which was significantly higher than the 0.61±0.08 AUC of ExtraTrees classifier on all initial variables (Figure 3 a)). With XGBoost operating on the 5-variable reduced dataset, a sensitivity of 83% and a specificity of 71% at the point optimizing the Youden index (sensitivity + specificity - 1) was reached (Figure 3 a)).

The AUC of a model solely based on sex and diameter in Tang et al. was 0.67 (95% CI, 0.58-0.77) with a sensitivity of 60% and a specificity of 77% (153). Rupture status prediction based on ExtraTrees on all initial variables yielded a lower AUC than Tang et al. (0.61 vs 0.67) but prediction based on XGBoost on the 5-variable reduced dataset beat Tang et al. AUC- wise (0.81 vs 0.67) and sensitivity-wise (83% vs 60%) but not specificity-wise (71% vs 77%).

The 5 variables ranked from most important to least important in helping XGBoost predict rupture were: neck presence, antiplatelet use, aneurysmal

calcification number, Euler distance between calcifications mean value, and Euler distance between calcifications standard deviation (Figure 3 b)).

These five variables highlighted by ExtraTrees correspond to variables that were significantly different between both groups in the univariable analysis. The relative importance in XGBoost classification mirrors the p-values that were obtained in the univariable analysis: neck presence ($p<0.0001$), antiplatelet use ($p<0.001$), aneurysmal calcification number ($p<0.01$), calcification Euler distance ($p< 0.059$). We could not compare calcification Euler distance standard deviation XGBoost importance and p-value given that it was not possible to compare standard deviations using student's t test.

Discussion

This study yielded a model that could more accurately discriminate ruptured from non-ruptured AAAs using machine learning. The 5-variable machine learning analysis led to an AUC of 0.81 and an optimal sensitivity of 83% and a specificity of 71%. It performed better than a model strictly based on sex and diameter in a similar study done at the same centers in the past by Tang et al. (60% sensitivity and 77% specificity (AUC 0.67)). Three of the 5 most important variables yielded by ExtraTrees Classifier were related to aneurysmal calcification (number, mean value and standard deviation of Euler distance between calcifications).

The counterintuitive improvement of AUC between the initial dataset and reduced dataset can possibly be attributed to the removal of “parasite variables” in the initial set that could have made it more difficult for the classifier to predict rupture.

The univariable analysis demonstrated that ruptured AAAs are less likely to have a neck, which is even more striking as we matched for sex, age and diameter, eliminating potential confounders in this relation. Hinchcliffe et al. found similar results as ruptured AAAs in their study had shorter infrarenal necks (220). A systematic literature review reported that patients with long AAA necks (>2.5 cm) had a 20% reduction in the rate of aneurysm rupture (56). Another study found that ruptured AAAs tend to have shorter necks in a cohort of unmatched patients (221).

As per our results, patients with a non-ruptured AAA were more likely to be treated by antiplatelets while in the literature, the effect of antiplatelet drugs on AAAs is controversial. Three clinical studies have suggested that ASA may mitigate the growth of AAAs (222-224) while the largest study on the subject (n=4010) found no association between ASA and AAA rupture risk as well as a higher 30-day ruptured AAA case-fatality rate for users of ASA (225).

After a series of trial and error segmentations at various density thresholds for calcifications, 500 HU was chosen. This threshold was a good compromise between the occurrence of calcification erosion with a higher density threshold and intravascular contrast contamination with a lower threshold. In the literature, de Weert et al. and Komen et al. also used a 500 HU threshold to respectively isolate carotid and iliac calcifications in C+ CT scans (205, 206).

Our results show that although calcification load between ruptured and non-ruptured AAAs is the same, repartition is different. Ruptured aneurysms were more likely to have their calcification load concentrated in a small number of clusters which are closer to each other. The literature is scarce and controversial regarding calcifications and AAA rupture risk. Two small clinical studies found results indicative of a possible protective effect to calcifications. Lindholt et al found significantly slower expansion rates of AAAs in 122 men with small aneurysms containing calcification in more than 50% of the total AAA wall circumference, matching for age, ASA and smoking(195). Nakayama et al. performed a retrospective cohort study on 414 patients with only C- CT scans which they segmented at a 130 HU threshold matching for AAA expansion.

Regression analysis with diameter matching, showed that AAA expansion was inversely correlated with the calcification index of the AAA measured at initial CT. The authors also found that an expansion exceeding 5 mm annually was significantly associated with a % calcification index of AAA <2.74% on the initial CT (201). Contrarily to our study, Nakayama et al. did not exclude intraluminal thrombus calcifications. On the other hand, a case–control study by Buijs et al. yielded findings that suggest a deleterious effect of calcifications on AAA stability. Regression analysis with age and sex matching demonstrated an overall significant odds ratio of 1.34 symptomatic or rupture risk increment per additional point of Abdominal Aortic Calcification-8 score (AAC-8) score, which is a less objective score than the semi-automated segmentation we did in our study (192).

The major limitation of our study was the heterogeneity of our patient population, which could be the main cause for the very large standard deviation of calcification variables (volume, surface, number). Some patients had heavily calcified AAAs while others had barely any calcifications. Although the 500 HU threshold heavily eroded calcification, the effect was non-differential through the dataset. In the worst case, erosion attenuated the correlation between calcifications and aneurysm rupture. Most of the patients with ruptured AAAs had a CT scan done after rupture which, perhaps could have slightly impacted the AAA morphology, although change in neck shape and maximal diameter after rupture would be highly unlikely.

Most finite-element studies for peak wall stress assume that an AAA wall is homogenous (226). Regardless of whether wall calcifications are protective or causative of AAA rupture, it is more and more clear that they cannot be ignored and should be incorporated in finite-element analysis models. To further investigate the relation between calcifications and AAA rupture, a larger prospective study with a standardized CT acquisition protocol and a standardized contrast density should be undertaken.

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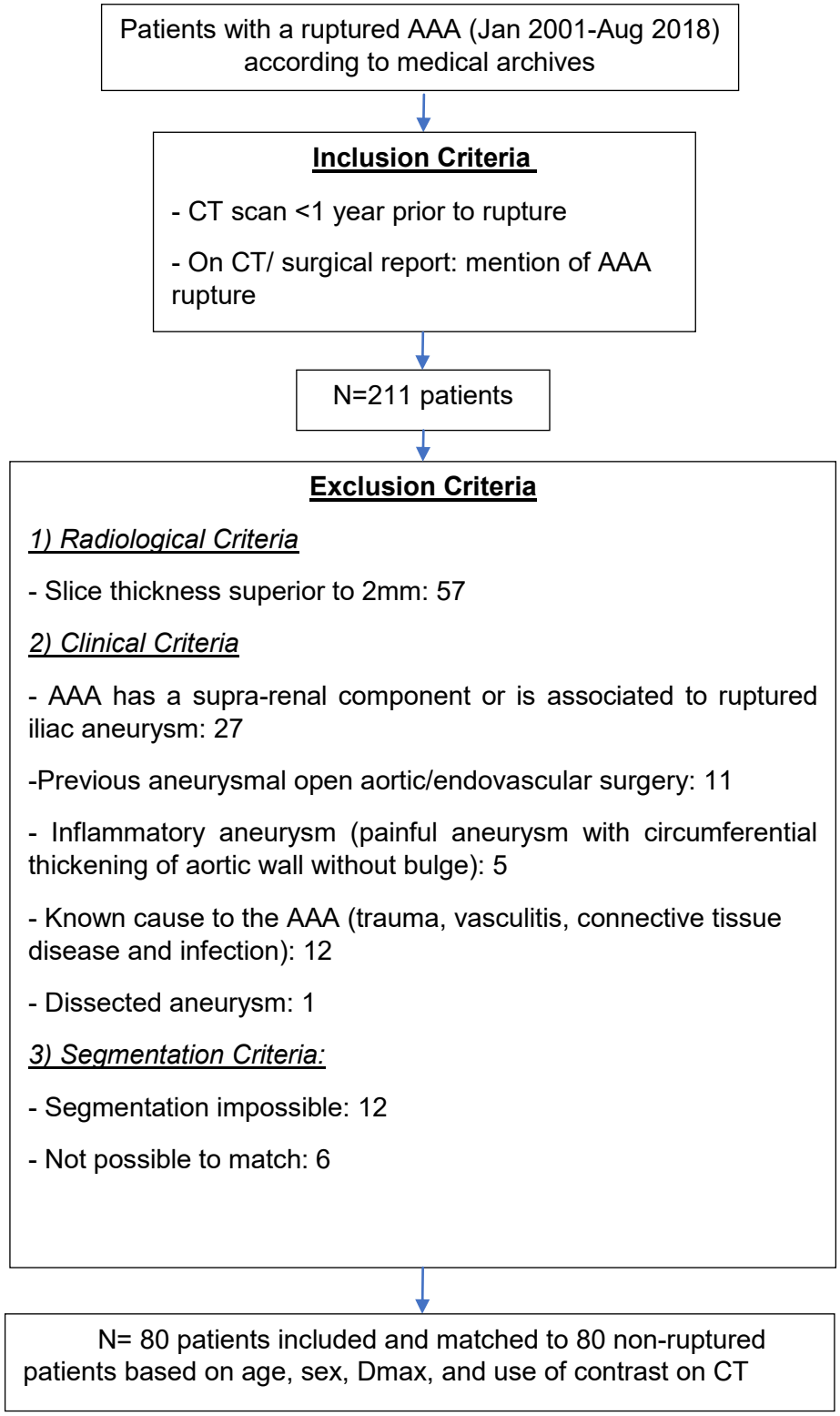

Figure 1- Study flowchart for patients with ruptured AAAs. Patients with ruptured AAAs were matched to patients with non-ruptured AAAs using trial and error.

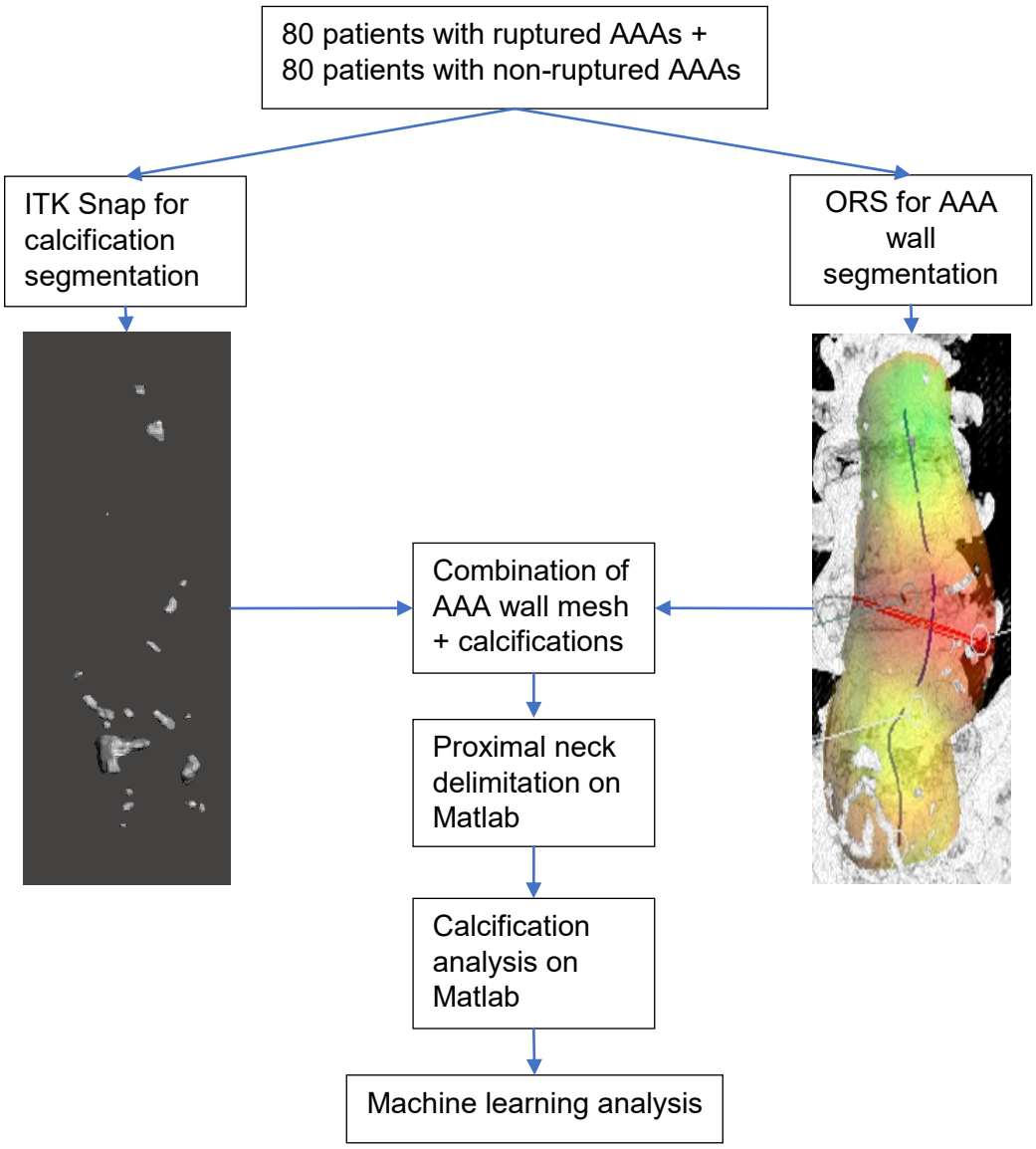

Figure 2 - Project workflow Left picture represents a segmented wall calcification of an infrarenal AAA on ORS (AAA wall segmentation software). Right picture represented a segmented AAA infrarenal wall. The black line represents the centerline and the red ellipse, the maximal diameter. Right picture represents segmented aortic wall calcifications on ITK Snap (AAA calcification segmentation software). Original work.

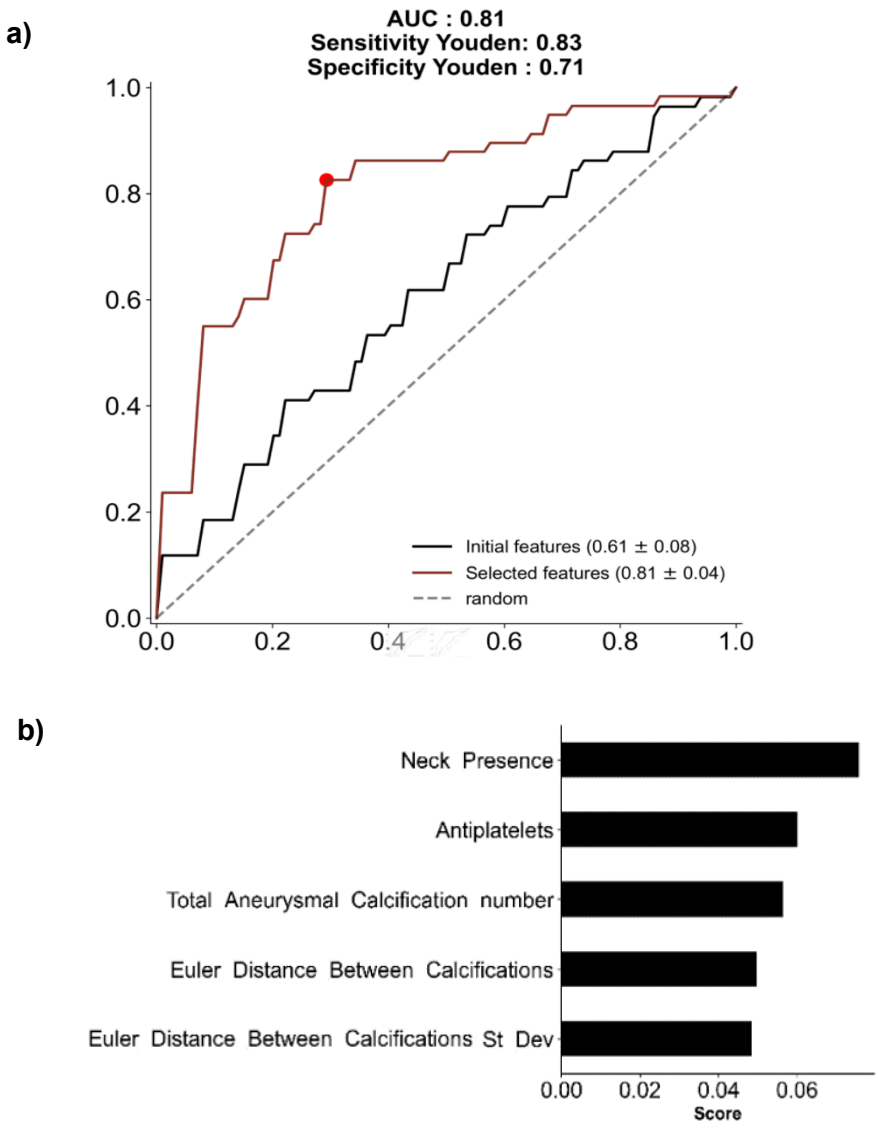

Figure 3 -

a) ROC-curves for rupture status classification

Black line is the ROC curve for rupture status prediction using ExtraTrees classifier on all initial variables (AUC 0.61±0.08)

Red line is the ROC curve for rupture status prediction using XGBoost classifier on the 5-variable reduced dataset (0.81±0.04)

b) Relative importance of 5-variable reduced dataset from XGBoost classifier

	Ruptured	Non-ruptured	P value	Number of patients	
				Ruptured	Non-ruptured
Age at index date (years)	73.9(8.3)	74.2(8.6)	0.826	80	80
Sex (% men)	71(89)	71(89)	1.000	80	80
CT scan to index date interval (days)	8.1(27.1)	48.5(69.1)	**<0.00001**	80	80
Tobacco smokers (%)	37(63)	47(64)	0.843	59	73
COPD (%)	19(32)	18(25)	0.337	59	73
Hypertension (%)	39(66)	55(75)	0.244	59	73
Diabetes Mellitus (%)	14(24)	19(26)	0.762	59	73
Coronary Artery Disease (%)	27(46)	39(53)	0.381	59	73
Dyslipidemia (%)	31(53)	43(59)	0.464	59	73
Chronic renal failure (%)	16(27)	20(27)	0.972	59	73
Beta blockers (%)	24(41)	43(59)	**0.037**	59	73
Anticoagulants (%)	24(41)	35(48)	0.404	59	73
Antiplatelets (%)	31(53)	58(80)	**0.001**	59	73
Lipid lowering drugs (%)	31(53)	55(75)	**0.006**	59	73

Table 1. Demographic profile of patients (Mean ± standard deviation or N (%)) An additional column representing N of patients with no missing data has been added.

	Ruptured (n=80)	Non-ruptured (n=80)	P value
Neck Presence (%)	36(45)	61(76)	**<0.0001**
Max AAA Diameter (mm)	80.8(17.6)	79.0(17.3)	0.505
Centerline Length (mm)	129.1(23.9)	131.5(19.5)	0.490
Calcification Volume (mm 3)	635(913)	689(893)	0.707
Calcification Surface (mm 2)	1008(1367)	1119(1290)	0.598
Calcification Number	18.0(17.9)	25.6(18.9)	**0.010**
Aneurysmal Wall Surface (mm^2)	25149(10290)	24541(8512)	0.684
Calcification Euler Distance (mm)	71.5(34.1)	80.7(26.6)	0.059

Table 2. AAA calcification statistics (mean ± standard deviation or N (%)) Euler distance is the average distance between every calcification with each other calcification, it is an index of calcification dispersion throughout the aneurysmal wall**.**

Appendix 1

Keywords for PACS search in both centers:

1) Aneursyms:
- Abdominal aortic aneurysm
- AAA
- Rupture
- Prerupture
- Bleb

2) CT configurations:
- Abdominal CT
- Abdominal-pelvic CT
- CT Angiography
- CTA
- Lower limb angioCT
- Lower limb angioscan
- CT Tevar - Evar F/U
- CT angio aortic dissection - abdomen/pelvis
- CT angio vascular -abdo/pelvis/extremity

Section 3 - Conclusion

In conclusion, the initial goal of the study was to find whether calcification load and distribution could help predict AAA rupture. The study has been carried out for three main reasons: AAA prevalence could increase in the future because of aging populations, sex and diameter are poor prognostic factors for individual personalized risk prediction, EVAR is not a benign intervention and requires an extensive follow-up, therefore only those patients who definitely need it should have it.

We hypothesized that indeed calcifications might be a predictor of AAA rupture. We made this assumption based on numerous papers in the literature not agreeing on whether calcifications might be protective against AAA rupture or not. Regardless of this question, it was clear throughout the literature that calcifications cannot be neglected when talking about AAAs.

Therefore, we went over 18 years of AAA data in two major tertiary centers to constitute a databank of 80 ruptured patients and matched them based on sex, age, diameter, and contrast to 80 non-ruptured patients. We found out in our univariable analysis that ruptured AAAs have similar volumes of calcifications but significantly less calcification aggregates. This means calcifications were more concentrated in fewer spots in ruptured aneurysms. Given the extensive matching we did prior to data analysis, this finding is substantial, as confounders like diameter cannot explain it. Three calcification variables (namely calcification number, calcification Euler distance and standard deviation) were among the top five variables that allowed the machine learning classifier to predict AAA rupture. Counterintuitively, the most important variable out of the five was neck presence, for which ruptured AAAs were much less likely to have as per the univariable analysis. Our prediction model performed much better than sex and diameter alone in the literature (153).

If neck and antiplatelet variables (i.e. variables not related to calcifications) were to be removed out of our set of five key variables, our model would yield a lower AUC given neck and antiplatelet are the two most potent variables in our model. This is why one needs to have reservations about this model, as the two most potent variables that allowed us to improve rupture prediction are not related in any way to aortic calcifications. In future studies, rupture prediction should be attempted with a wide array of clinical, morphologic, physical (wall stress, etc.) and physiological (inflammation, calcifications, etc.) variables. The integration of these multiple types of variables in one model could constitute our best strategy at improving AAA rupture prediction.

With this new study, it is more and more clear that calcifications cannot be neglected when modeling an AAA wall for simulation purposes. This study confirms the important role that calcifications play in an AAA. For instance, most finite-element studies for peak wall stress assume that an AAA wall is homogenous, and this is bound to change in light of this study and others proving the importance of calcifications in AAAs (226).

The long-term impacts of this study could be, if our findings are reproduced in a larger study, the creation of a PACS plug-in that, based on AAA morphology and calcification dispersion, could yield a prognosis for rupture and recommendations for intervention. This larger study should follow a prospective design and be carried out in multiple centers. There should be a common C+ CT scan protocol and a standardized low-density IV contrast to allow for better calcification segmentation. Also, if it would yield similar results with the same algorithm, this future study would dismiss any doubts on overfitting from our model.

Section 4 – References

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