MACD - an Imaging Marker for Cardiovascular Disease

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\textbf{ABSTRACT}

Despite general acceptance that a healthy lifestyle and the treatment of risk factors can prevent the development of cardiovascular diseases (CVD), CVD are the most common cause of death in Europe and the United States. It has been shown that abdominal aortic calcifications (AAC) correlate strongly with coronary artery calcifications. Hence an early detection of aortic calcified plaques helps to predict the risk of related coronary diseases. Also since two thirds of the adverse events have no prior symptoms, possibilities to screen for risk in low cost imaging are important. To this end the Morphological Atherosclerotic Calcification Distribution (MACD) index was developed.

In the following several potential severity scores relating to the geometrical outline of the calcified deposits in the lumbar aortic region are introduced. Their individual as well as their combined predictive power is examined and a combined marker, MACD, is constructed. This is done using a Cox regression analysis, also known as survival analysis. Furthermore we show how a Cox regression yields MACD to be the most efficient marker. We also demonstrate that MACD has a larger individual predictive power than any of the other individual imaging markers described. Finally we present that the MACD index predicts cardiovascular death with a hazard ratio of approximately four.

\textbf{Keywords:} Cardiovascular diseases, abdominal aortic calcifications, radiographs, imaging biomarkers, Cox regression analysis

1. INTRODUCTION

Cardiovascular diseases (CVD) are the most common cause of death in Europe\textsuperscript{1} and the United States.\textsuperscript{2} This is the case despite general acceptance that a healthy lifestyle and the treatment of risk factors can prevent the development of CVD.\textsuperscript{3} It is known that abdominal aortic calcifications (AAC) are strong predictors of cardiovascular morbidity and mortality.\textsuperscript{4} They correlate strongly with coronary artery calcifications and can hence predict the risk of coronary artery problems.\textsuperscript{5}

While other imaging modalities, also have developed surrogate markers of CVD, like carotid IMT or CAC, a clear advantage of using standard radiographs is the availability of large, long duration studies from osteoporosis screenings.\textsuperscript{6,7} Such historical data can be used to verify AAC markers. Also since two thirds of the adverse events have no prior symptoms, possibilities to screen for risk in low cost imaging are important.

A common method to quantify CVD risk clinically is the Framingham Aortic Calcification score (AC24)\textsuperscript{8} used on lumbar aortic radiographs. One constructs the AC24 score by first projecting the AACs to the aorta wall they are associated with, while disregarding calcifications in the middle of the aorta. Then each vertebra is successively graded after the degree of lesion occupation: 0 for no AAC, 1 for AACs filling less than $\frac{1}{3}$ of the wall they are projected on, 2 for AACs filling more than $\frac{1}{3}$ but less than $\frac{2}{3}$ in the projection, and 3 for a $\frac{2}{3}$ occupation of the wall of the AACs. This is illustrated in Fig. 1.
1.1 New AAC Markers

We believe that there is more information to gain from the AACs. Therefore several potential severity scores relating to the geometrical outline of the calcified deposits in the lumbar aortic region were examined:

- **Area (ArP):** The area percentage of the projected aorta wall occupied by AACs.
- **Simulated area percentage (SiArP):** Since X-ray analysis only visualises the calcified core and not the biological extent of the AACs, we estimated the size of the atherosclerotic inflammation from the area percentage and form of the observed AACs. The extent of the atherosclerotic inflammation was simulated by using a grass-fire equation implemented by a morphological dilation with a circular structuring element of radius 200 pixels (corresponding to 8.9 mm). The size of the structuring element was confirmed to be biologically sensible by comparing with histology observations. An illustration is given in Fig. 2. The simulated area percentage is the percentage of the projected lumbar aorta covered by the simulated plaques including both calcified core and simulated inflamed area.
- **Thickness Percentage (ThiP):** The average thickness of the AACs along the aorta wall relative to the aorta width.
- **Wall Percentage (WallP):** The percentage of the lumbar aorta wall covered by AACs.
- **Length Percentage (LenP):** The fraction of the length of the lumbar aorta where AACs are present.
- **Number of Calcified Deposits (NCD):** The number of distinct AACs.

After quantifying the above AAC markers based on manual annotations, we examined statistically using multivariate Cox regression which of them supply each other and which are independent of each other in order to build a combined, more informative marker.
1.2 Possible Automation

Although the current analysis is based on manual annotations by trained radiologists, the annotation procedure can in principle be automated. A first step toward automated detection and segmentation of aortic calcifications from radiographs has been published by de Bruijne\textsuperscript{10} and Lauze, F. et al.\textsuperscript{11}

2. METHODS

2.1 Study Population

The data was collected from the EPI Followup study which was part of the multi-centered PERF study.\textsuperscript{12} This study addressed the role of a number of metabolic risk factors in the pathogenesis of CVD and osteoporosis\textsuperscript{13} and was carried out by the Center for Clinical and Basic Research (CCBR, Ballerup, Denmark) in 1992 and 2001. The available data consists of Baseline images of 308 subjects. Of these at Baseline (1992) 187 X-rays have some or none aortic calcifications present and the rest comprises a control group of 121 patients with no calcifications at Baseline and Followup. Subsequently, there exist 135 X-ray images where all have calcifications and the same control group of 121 patients without calcifications at Followup (2001). 52 people died between Baseline and Followup due to cancer (n=27), CVD (n=20) or other causes (n=5), whereby the information about the mortality status was obtained via the Central Registry of the Danish Ministry of Health. A schematic overview of the study population can be seen in Fig. 3.

At Baseline, demographic information and CVD risk parameters such as age, weight, height, body mass index (BMI), waist and hip circumferences, systolic and diastolic blood pressure (BP), treated hypertension, treated diabetes, smoking, regular alcohol and daily coffee consumption, and weekly fitness activity were collected. Using a blood analyzer (Cobas Mira Plus, Roche Diagnostics Systems, Hoffman-La Roche, Basel, Switzerland), measurements of fasting glucose and lipid profile (total cholesterol, triglycerides, LDL-cholesterol (LDL-C), HDL-cholesterol (HDL-C), and apolipoprotein (ApoA and ApoB)) were obtained.

The lateral X-ray images of the lumbar aorta (L1-L4) were digitized in 2007/2008 using a Vidar Dosimetry Pro Advantage scanner (Vidar, Herndon, USA) providing an image resolution of 9651 × 4008 pixels on a 12-bit gray scale with a pixel size of 44.6µm × 44.6µm. Three trained radiologists without prior knowledge of the patients conditions annotated the vertebrae, the aorta and the calcifications in the digitized images. They used...
2.2 Marker selection and combination

The marker selection is done with the help of a Cox regression analysis, also known as survival analysis. A basic overview is given in, while a thorough coverage of the subject can be found in.

The basis of the Cox regression model is the examination of the behavior of the hazard function with respect to certain environmental parameters. The hazard function is given by

$$h(t; z_i) = h_0(t) \exp(z_i^T \beta),$$  \hspace{1cm} (1)

where \( t \) is the time and \( z_i \) with \( i = 1, \ldots, n \) are the \( q \)-dimensional environmental parameter vectors for each individual patient \( i \) in the study. \( h_0 \) is an unknown baseline hazard function used to model the hazard without environmental influences. \( \beta \) is a \( q \)-dimensional vector giving the coefficient estimates of a Cox regression of the result status (e.g. dead or alive) to the predictors in \( z_i \). The Cox regression tries to estimate the regression parameters \( \beta \) and measure their significance.

In all Cox regression analyses, we use the marker values for the complete population of 308 patients and vary the binary outcome variable (e.g. CVD dead = 1, alive or other dead = 0) according to the group of interest we focus on.

First we used Cox regression analysis on the image markers to test their individual prognostic power. In the Cox regression the outcome variable was the time of death and survivors were right censored. Furthermore we build a Cox regression model with all variables and then successively deleted the least significant marker until only significant markers were left. Hereby significance of the marker \( q \) was given as the model weight \( \beta_q \) being significantly different from zero. This way single markers that complement each other could be found and a combined and more informative marker constructed.
Figure 4. An X-ray image from the study population: First, the original X-ray image is displayed, then the X-ray with the manual annotation overlaid. In blue the vertebra points are shown, in green the outline of the lumbar aorta and in red the AAC.
Table 1. The mean ± one standard deviation of all the imaging markers stratified for the different subsets of patients.

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Survivors (n=308)</th>
<th>CVD (n=20)</th>
<th>Cancer (n=27)</th>
<th>CVD/Cancer (n=47)</th>
<th>Other (n=5)</th>
<th>All-cause (n=52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC24</td>
<td>1.67 ± 2.55</td>
<td>1.35 ± 2.34</td>
<td>3.50 ± 2.35</td>
<td>3.41 ± 3.23</td>
<td>3.45 ± 2.86</td>
<td>1.35 ± 2.36</td>
<td>3.23 ± 2.86</td>
</tr>
<tr>
<td>ArP</td>
<td>0.6 ± 1.2</td>
<td>0.5 ± 1.1</td>
<td>1.0 ± 0.9</td>
<td>1.6 ± 1.8</td>
<td>1.3 ± 1.5</td>
<td>0.5 ± 1.1</td>
<td>1.2 ± 1.5</td>
</tr>
<tr>
<td>SiArP</td>
<td>11 ± 17</td>
<td>8.9 ± 15.7</td>
<td>24 ± 16</td>
<td>25 ± 24</td>
<td>25 ± 21</td>
<td>8.7 ± 15.5</td>
<td>23 ± 21</td>
</tr>
<tr>
<td>ThiP</td>
<td>11 ± 20</td>
<td>9.0 ± 19</td>
<td>17 ± 16</td>
<td>25 ± 28</td>
<td>21 ± 24</td>
<td>8.7 ± 19</td>
<td>20 ± 24</td>
</tr>
<tr>
<td>WallP</td>
<td>1.03 ± 1.83</td>
<td>0.79 ± 1.64</td>
<td>2.08 ± 1.70</td>
<td>2.51 ± 2.68</td>
<td>2.33 ± 2.30</td>
<td>0.80 ± 1.63</td>
<td>2.16 ± 2.27</td>
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<tr>
<td>LenP</td>
<td>7.5 ± 12.8</td>
<td>6.0 ± 11.7</td>
<td>15.4 ± 11.2</td>
<td>17.3 ± 17.6</td>
<td>16.5 ± 15.1</td>
<td>5.9 ± 11.6</td>
<td>15.4 ± 15.0</td>
</tr>
<tr>
<td>NCD</td>
<td>3.8 ± 7.7</td>
<td>2.6 ± 6.4</td>
<td>8.5 ± 6.5</td>
<td>11.6 ± 13.4</td>
<td>10.3 ± 11.0</td>
<td>2.6 ± 6.3</td>
<td>9.6 ± 10.8</td>
</tr>
</tbody>
</table>

3. RESULTS

First we examine the imaging markers we have gathered. Their means and respective standard deviations can be found in Table 1. One can easily see that they all have a relation to identifying the people that are dying of CVD or CVD/Cancer, because all markers show elevated values in these groups.

But how well can the markers assess the risk of dying from CVD or CVD/Cancer? In other words, how well can the markers differentiate the groups CVD and CVD/Cancer deaths from the rest?

In order to test this we use a Cox regression analysis to test their individual prognostic power. We fit a Cox regression model to each marker where the time of death is the outcome variable and survivors are right censored. We do this for each marker by itself, but also for each marker adjusted with three different sets of biological variables: a model consisting of age, smoking status and triglyceride levels as well as the SCORE\(^7\) and Framingham\(^8\) scores. The SCORE is a combination of the age, the smoking status, the levels of the total cholesterol and the systolic blood pressure, while the Framingham score is comprised of the same variables plus the HDL cholesterol and the hypertension treatment status.

We adjust by first making a Cox regression model including only the biological variables that we want to adjust for, e.g. the SCORE. Then we combine the biological variables into one new variable by a linear weighing with their \( \beta \)-weights derived by the Cox regression. The last step is to take this new variable and build a new Cox regression model including the imaging marker we want to adjust. The resulting \( \beta \)-weight for the imaging marker in the new Cox regression model gives rise to the biologically adjusted prognostic power.

Table 2 shows that the simulated area percentage and NCD have the largest individual predictive power. Their hazard ratio is 2 and highly significant even after adjusting for the three different biological models. So the ratio of the probability of dying in the CVD or CVD/Cancer death group versus the rest is significantly larger than 1. We keep in mind that SiArP and NCD have the largest individual predictive power.

The next step is to test the combined predictive power of the seven imaging markers. This is again done by fitting a Cox regression model where the time of death is the outcome variable and survivors are right censored. But now one successively deletes the marker with the least significant \( \beta \)-value and proceeds until only markers with significant \( \beta \)-values are left. This can be seen for the CVD and the CVD/Cancer group in Table 3. First the non-adjusted hazard ratios from Table 2 are stated again and then two elimination models are shown. When combining the markers in a Cox regression model only area percentage and NCD remain. What happened to the simulated area percentage? It is actually the last marker to be deleted in the elimination model.
To summarize, there are three different markers that exhibit statistical predictive power: area percentage, simulated area percentage and number of calcified deposits. From the $\beta$-values of the different models the correlation to the risk of dying can be read. A negative $\beta$-value implies that the marker is correlated to the risk of death. A positive $\beta$-value shows that the marker is positively correlated to the risk of death. With this knowledge we can build two more predictive markers out of the area percentage, the simulated area percentage and the number of calcified deposits:

1. Morphological Atherosclerotic Distribution (MAD) factor: The simulated area percentage divided by the area percentage.

To test their individual predictive power again the hazard ratio was calculated for the non-adjusted markers and an adjustment after the above used three biological models. This can be seen in Table 4.

Both the MAD factor and the MACD index now have a larger individual predictive power than any of the other individual markers displayed before. Notably the MACD index contains a hazard ratio of approximately four through all categories. Therefore the index is very potent at identifying the CVD death group, which is exactly what we want it to do.
Table 3. The individual hazard ratio values for the markers in the CVD and the CVD/Cancer group as well as two Cox regression elimination models. The symbols *,**, and *** denote the significance corresponding to $p < 0.05$, $p < 0.01$ and $p < 0.001$, respectively.

<table>
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<tr>
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<tbody>
<tr>
<td>MAD</td>
<td></td>
<td></td>
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<tr>
<td>CVD</td>
<td>3.37 (1.83-6.21) ***</td>
<td>2.44 (1.22-4.89)*</td>
<td>3.02 (1.55-5.86)**</td>
<td>2.85 (1.44-5.64)**</td>
</tr>
<tr>
<td>CVD/cancer</td>
<td>2.19 (1.58-3.04) ***</td>
<td>1.58 (1.11-2.26)*</td>
<td>1.83 (1.29-2.59)***</td>
<td>1.74 (1.22-2.48)***</td>
</tr>
<tr>
<td>MACD index</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVD</td>
<td>5.22 (2.40-11.36) ***</td>
<td>3.17 (1.48-6.78)**</td>
<td>4.36 (1.97-9.66)***</td>
<td>4.22 (1.79-9.97)***</td>
</tr>
<tr>
<td>CVD/cancer</td>
<td>2.99 (2.05-4.35) ***</td>
<td>2.01 (1.37-2.95)***</td>
<td>2.43 (1.64-3.59)***</td>
<td>2.27 (1.51-3.41)***</td>
</tr>
</tbody>
</table>

Table 4. The hazard ratio per standard deviation increase for MAD and MACD stratified into death cause and adjusted for physical/metabolic markers, EU Score and Framingham score respectively. The symbols *,**, and *** denote the significance corresponding to $p < 0.05$, $p < 0.01$ and $p < 0.001$, respectively.

4. CONCLUSION AND FUTURE WORK

As shown above, simple statistical modeling can help to identify potential imaging markers as a combination of basic markers. Further steps can be taken by building combined biological and imaging markers or by developing even more AAC markers and repeating the same procedure as above.

Of course one is left to show the clinical applicability and reproducibility of the identified marker, but for marker development this statistical approach seems to be a step in the right direction.

5. ACKNOWLEDGMENTS

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REFERENCES