ABSTRACT

CT-based coronary artery calcium (CAC) scanning has been introduced as a non-invasive, low-radiation imaging technique for the assessment of the overall coronary arterial atherosclerotic burden. A three dimensional CAC volume contains significant clinically relevant information, which is unused by conventional whole-heart CAC quantification methods. In this paper, we have developed a more detailed distance-weighted lesion-specific CAC quantification framework that predicts cardiac events better than the conventional whole-heart CAC measures. This framework consists of (1) a novel lesion-specific CAC quantification tool that measures each calcific lesion’s attenuation, morphologic and geometric statistics; (2) a distance-weighted event risk model to estimate the risk probability caused by each lesion, and (3) a Naive Bayesian technique for risk integration. We have tested our lesion-specific event predictor on 30 CAC positive scans (10 with events and 20 without events), and compared it with conventional whole-heart CAC scores. Experiment results showed our novel approach significantly improves the prediction accuracy, including AUC of ROC analysis was improved from 66 ∼ 68% to 75%, and sensitivities was improved by 20 ∼ 30% at the cutpoints of 80% specificity.

Index Terms— Coronary Artery Calcium, Lesion Specific, Cardiac Event Prediction

1. INTRODUCTION

Atherosclerosis, the leading cause of morbidity and mortality worldwide, is a complex disease initiated and propagated by lipoprotein deposition and inflammation. Later stages of atherosclerosis are characterized by progressive deposition of calcium in the coronary arterial vessel-wall. Histopathology, computed tomography and intravascular ultrasound studies have confirmed that the extent of coronary calcification is closely correlated to the atherosclerosis plaque burden. CT-based coronary artery calcium (CAC) scanning [1, 2] is a three dimensional imaging technique that has been introduced as a non-invasive, low-radiation method for the assessment of the overall coronary arterial atherosclerotic burden, by quantifying calcium in the coronary vasculature. The conventional whole-heart Agatston score (AS) [3] and volume score (VS) [4] of CAC have been validated to be independent of, and additive to, the Framingham Risk Score (FRS) [5] in predicting major cardiovascular events [6]. CAC is also considered safer and more appropriate for the primary prevention setting than invasive modalities, such as intravascular ultrasound (IVUS), and non-invasive and high-radiation modalities, such as CT angiography.

A three dimensional CAC volume contains significant clinically relevant information, such as the number of involved vessels, the number of plaque lesions, lesions’ distribution, and each lesion’s size and shape. However, such information is left unused by current whole-heart AS/VS measurements. Therefore, our hypothesis is that a more detailed lesion-specific CAC evaluation is more predictive of major adverse cardiac events than the conventionally used whole heart AS/VS. In this paper, we have developed a novel lesion-specific CAC quantification software, using which we are able to measure each lesion’s geometric and morphologic parameters. Based on these measurements, we have developed a distance-weighted lesion-specific risk assessment algorithm to improve the predictive value of CAC scan for the incidences of major adverse cardiac events (MACE), by modeling and optimizing the risk from each individual lesion and combining them using a Naive-Bayesian technique.

Our method has been assessed using 30 CAC positive data that consists of 10 patients with major adverse cardiac events within 2 years after the CAC scan and 20 patients without events within 2 years after the CAC scan. We found that FRS and whole-heart CAC measurements were similar in patients with/without events. However, our distance-weighted lesion-specific measures were significantly different using an unpaired t-test. From the optimized risk model of the individual plaque, we found that most culprit lesions in our model located in the proximal 3 ∼ 4cm segments of the right coronary artery and the left circumflex artery, respectively, which is in good accord with clinical observations [7].

2. METHODOLOGY

2.1. Lesion-specific CAC quantification software

In order to measure lesion-specific CAC parameters, we have developed a software that has been successfully tested
on CAC scans from two clinical CT scanners (Siemens 64-MDCT and Toshiba 320-MDCT), which has a convenient graphical user interface, as shown in Figure 1, that allows users to interactively identify and label the coronary calcific lesions and the ostia of 4 major coronary arteries, including the left main coronary artery (LM), the left anterior descending artery (LAD), the left circumflex artery (LCx) and the right coronary artery (RCA), as shown in Figure 2. For lesions that cover two or more arteries, we define their corresponding artery as the more proximal one. For example, if a lesion is located at the ostium of LAD and LCx, and covers all three LM, LAD and LCx arteries, we label this lesion as LM.

Calcification is detected using the conventional Hounsfield unit thresholding method with a predefined threshold equaling 130HU, i.e., all voxels with intensity ≥ 130HU are classified as calcium. Our software also provides an option to adjust this threshold value. Starting from the user-annotated seed point in a calcific lesion, the software propagates in 3D and segments the corresponding lesion using a 3D flood-fill operation. This 3D flood-fill operation propagates through 2D slices using a 6-connectiveness criterion, so that physicians don’t need to label the lesion slice by slice as in most clinically used software. In this way, our method can vastly expedite the image analysis process, with which a physician is able to analyze a set of CAC scan in less than 5 minutes.

Fig. 1. The graphical user interface of the software. (A) is the editable field to adjust the HU threshold of calcific regions. (B) is the status panel. From the status illustrated in the figure, the user needs to label three arterial ostia. (C) is an example of the annotated calcific lesions, which is encoded in purple. From the label illustrated in (C), this is the 6th lesion in the LAD artery. (D) is the right-click popup menu.

For each segmented lesion, our software will automatically measure its morphologic and geometric statistics, such as the 2D/3D lesion-specific AS and VS, width, length, average and maximum Hounsfield value, and the Euclidian distance to its corresponding artery’s ostium. Finally, these parameters will be output to a clinical report. Our 3D Agatston scoring method is similar to the original 2D one [3], except that we will use the whole 3D volume and the highest HU value in the whole 3D lesion, instead of calculating 2D Agatston scores slice by slice, and adding them up. In this paper, in order to predict MACE risk and compare with the whole-heart AS/VS measurements, we will focus on using the parameters of the lesion-specific AS and VS, and the Euclidian distance to the lesion’s corresponding ostium.

2.2. Risk model of cardiac events

Although the whole-heart CAC scores, which represent the overall calcification burden in the heart, are proven risk indicators of cardiac events, the distribution and the lesion-specific details of the calcification has a potential to play an additive and indispensable role in determining the extent and severity of the coronary disease. Intuitively, each calcific lesion can be modeled to be associated with a lesion-specific risk that leads to a cardiac event. In order to evaluate the overall event risk caused by all of the calcific lesions presented in the CAC scan, we combine the lesion-specific risks using a Naive Bayesian model, which assumes that the event risks caused by the lesions are independent to each other. Suppose there are a total number of $N$ calcific lesions presented in the heart. The overall event risk (probability) $P$ can be modeled as:

$$P = 1 - \prod_{i=1}^{N} (1 - p_i)$$

where $p_i$ is the event risk (probability) caused by lesion $i$.

For each calcific lesion, we design a distance-weighted lesion-specific AS/VS prediction model, assuming a sigmoid-shaped increasing relationship between event risk and the lesion-specific AS/VS, and a sigmoid-shaped decreasing relationship between event risk and the distance to ostium, where the sigmoid shapes are modeled by single-sided Gaussian curves. The intuition behind this model is that it is believed that the event risk associated with a lesion is determined by its AS/VS and location. The AS or VS quantifies the severity of the lesion itself; the distance to the corresponding ostium quantifies the lesion’s relevance to the whole heart, because the shorter distance, the more myocardium will be affected by the diseased artery. For a lesion $i$, suppose its lesion-specific
AS or VS is $s_i$, and its distance to the corresponding ostium is $d_i$, the event probability caused by this lesion can be modeled as:

$$p_i = \begin{cases} a_i \cdot \exp\left(-\frac{s_i^2}{2\sigma_s^2}\right), & \text{if } s_i > 3\sigma_s \\ a_i \cdot \exp\left(-\frac{s_i^2}{2\sigma_s^2}\right) \cdot \exp\left(-\frac{(s_i-3\sigma_s)^2}{2\sigma_d^2}\right), & \text{if } s_i \leq 3\sigma_s \end{cases}$$

where $a_i$ is a coefficient that adjust the probability level, and $0 < a_i \leq 1$, $\sigma_s$ and $\sigma_d$ are the Gaussian standard deviations of the AS/VS and distance sigmoid-shaped models. Each of the 4 major coronary arteries has its own specific $\sigma_d$, because they supply different cardiac territories with different importance. For LM, we set $\sigma_d^{LM} = +\infty$, because LM is short and important, supplying both LAD and LCx.

For the 30 CAC positive scans, we calculated their overall event risk $P_k$ ($k = 1, 2, \ldots, 30$) using Equations 1 and 2. We optimized the event predictor by tuning parameters $a_i$, $\sigma_s$, $\sigma_d^{LAD}$, $\sigma_d^{LCx}$, and $\sigma_d^{RCA}$ to achieve the smallest $p$-value of $P_k$ between patients with and without events using a unpaired t-test with unequal sample sizes and unequal variance:

$$t = \frac{\bar{P}_{\text{event}} - \bar{P}_{\text{no-event}}}{\sqrt{\frac{s^2_{\text{event}}}{10} + \frac{s^2_{\text{no-event}}}{20}}}$$

$$v = \frac{(s^2_{\text{event}}/10 + s^2_{\text{no-event}}/20)^2}{(s^2_{\text{event}}/10)^2/9 + (s^2_{\text{no-event}}/20)^2/19}$$

$$\{a_i, \sigma_s, \sigma_d^{LAD}, \sigma_d^{LCx}, \sigma_d^{RCA}\} = \arg\min_{a_i, \sigma_s, \sigma_d^{LAD}, \sigma_d^{LCx}, \sigma_d^{RCA}} \mathbf{B}\left(\frac{v}{v + t^2}, \frac{1}{2}, \frac{1}{2}\right)$$

where $\bar{P}_{\text{event}}$ and $\bar{P}_{\text{no-event}}$ are the means of the $P_k$s of the 10 patients with cardiac events and the 20 patients without event, respectively, and similarly, $s^2_{\text{event}}$ and $s^2_{\text{no-event}}$ are $P_k$s’ standard deviations. $\mathbf{B}$ is the incomplete beta function. The optimization is implemented through a brutal force approach with multiple resolutions and a local gradient-descent refinement step, which make the convergence faster.

3. RESULTS

Utilizing the lesion-specific CAC quantification software and the event risk model, we derived the optimized overall distance-weighted lesion-specific Agatston score and volume score (DWLS-AS/DWLS-VS) from the 30 CAC scans. We compared Framingham Risk Score (FRS), total-AS, total-VS, DWLS-AS, and DWLS-VS between patients with and without events using unpaired t-test and ROC analysis. As shown in Table 1, we found that FRS, total AS/VS were similar in patients with and without events. However, DWLS-AS/VS were significantly different ($0.1078 \pm 0.055$ vs. $0.0607 \pm 0.043$; $p=0.03$, and $0.1085 \pm 0.055$ vs. $0.0611 \pm 0.044$; $p=0.03$). As shown in Figure 3, the areas under the ROC curve (AUC) of DWLS-AS/VS were both 75%, which are significantly larger than the AUC of total-AS/VS, which were 64% and 66%. At the specificity point of 80%, which is commonly used as the clinical cutoff for choosing interventional treatment, the sensitivity of our DWLS-AS/VS measurements are 20% ~ 30% higher than the whole-heart scores.

<table>
<thead>
<tr>
<th></th>
<th>Mean±SD (Event vs. No Event)</th>
<th>p-Value</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total AS</td>
<td>826.5±819.2 vs. 539.8±687.1</td>
<td>0.3553</td>
<td>0.643</td>
</tr>
<tr>
<td>Total VS</td>
<td>683.8±642.3 vs. 480.0±628.0</td>
<td>0.4201</td>
<td>0.652</td>
</tr>
<tr>
<td>FRS</td>
<td>6.44±4.61 vs. 6.30±4.89</td>
<td>0.9399</td>
<td>0.500</td>
</tr>
<tr>
<td>DWLS-AS</td>
<td>0.1078±0.055 vs. 0.0607±0.043</td>
<td>0.0317</td>
<td>0.750</td>
</tr>
<tr>
<td>DWLS-VS</td>
<td>0.1085±0.055 vs. 0.0611±0.044</td>
<td>0.0315</td>
<td>0.750</td>
</tr>
</tbody>
</table>

Table 1. Statistics of different calcium quantification measurements in patients with and without cardiac event. Distance weighted lesion-specific (DWLS) AS/VS scores (bold) are significantly different ($p = 0.03$) in patients with/without event, which could be of event-predictive value.

In Table 2, we list the parameters derived from the optimization process of the DWLS-AS/VS models. We find that the more proximal calcified lesions have higher marginal risks of cardiac events in LCx and RCA, where $\sigma_d^{LCx} = 12.6\text{mm}$ in DWLS-AS, $\sigma_d^{LCx} = 12.1\text{mm}$ in DWLS-VS, $\sigma_d^{RCA} = 10.1\text{mm}$ in DWLS-AS, and $\sigma_d^{RCA} = 10.0\text{mm}$ in DWLS-VS. Suppose $3\sigma$ is the cutoff point of the Gaussian model, then most of the culprit lesions locate within the proximal 3 to 4 cm segments of the LCx and RCA, which is in good accord with clinical observations [7]. For LAD, we observe that $\sigma_d^{LAD}$ of DWLS-AS/VS are both $> 100\text{cm}$, which shows that lesions in LAD have the same high marginal event probability as in LM, in regard of their geometric locations. This is in accord
with clinical observations as well: LAD is a more important major coronary artery that supplies the largest cardiac territory; physicians tend to choose revascularization treatment, which is one instantiation of MACE, for LAD atherosclerosis, even if the plaque location is relatively dismal. $\sigma_s$ is the standard deviation of the AS/VS scores. As shown in Figure 4, $\sigma_{s-AS}$ is larger than $\sigma_{s-VS}$, since AS is usually larger than VS. It is also interesting to observe that in the single-lesion AS/VS ranges of 0 ~ 1000, which are most common in clinical CAC scans, the marginal risk probability and the AS/VS score have an approximate linear relationship, which agrees with the findings in the whole-heart CAC AS/VS studies [6].

### Table 2. The $\sigma_d$ and $\sigma_s$ values of DWLS-AS/VS.

<table>
<thead>
<tr>
<th></th>
<th>$\sigma_d$</th>
<th>$\sigma_d^{LAD}$</th>
<th>$\sigma_d^{LCx}$</th>
<th>$\sigma_d^{RCA}$</th>
<th>$\sigma_s$</th>
</tr>
</thead>
<tbody>
<tr>
<td>DWLS-AS</td>
<td>3030</td>
<td>&gt; 100cm</td>
<td>12.6 mm</td>
<td>10.1 mm</td>
<td>1</td>
</tr>
<tr>
<td>DWLS-VS</td>
<td>2301</td>
<td>&gt; 100cm</td>
<td>12.1 mm</td>
<td>10.0 mm</td>
<td>1</td>
</tr>
</tbody>
</table>

Fig. 4. The marginal probabilities versus (a) $\sigma_d$ and (b) $\sigma_s$ curves of DWLS-AS/VS.

### 4. DISCUSSION

Our experimental results agree with clinical observations very well, which demonstrates the effectiveness of our proposed method. Our distance-weighted lesion-specific CAC quantification method has two major components: 1) a distance-weighted model for each single plaque induced risk, and 2) a Naive Bayesian method to integrate risks. In component 1, the reason we used Euclidian distance, instead of the distance along the artery pathway, is that in non-contrast CAC scans, the artery pathway is difficult to identity. Manual annotation usually leads to less reproducibility. On the other hand, we have compared several CAC and contrast-enhanced CT angiography images, and found that the Euclidian distance and the distance along the artery pathway roughly have a linear relationship in LAD and LCx. In proximal and middle RCA, the relationship is also approximately linear. These observations validate our approach of using Euclidian distance. In component 2, the reason we used the Naive Bayesian model, instead of more complex methods that allow dependence among plaques, is that our training sample size is limited to 30. In order to avoid overfitting, we decided to choose a simpler model. For future work, we plan to develop a more complicated algorithm that allows plaque dependence on a much larger clinical cohort, such as the SPARC [8] data set, which will include 600 symptomatic patients.

### 5. CONCLUSION

In this paper, we have proposed a distance-weighted lesion-specific CAC quantification framework that predicts MACE better than the conventional whole-heart CAC measures, which suggests that a three dimensional CAC volume contains significant clinically relevant information, other than the whole-heart CAC scores. A more detailed and more comprehensive lesion-specific CAC evaluation extracts incremental information from routine CAC scans, and has the potential to significantly improve the clinical predictive value of CAC.

### 6. REFERENCES


