Diagnostic value of using epicardial fat measurement on screening low-dose chest CT for the prediction of metabolic syndrome

A cross-validation study

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Abstract

There has been a marked increase in the use of low-dose computed tomography (LDCT) for lung cancer screening. However, the potential of LDCT to predict metabolic syndrome (MetS) has not been well-documented in this risk-sharing population. We assessed the reliability of epicardial fat volume (EFV) and epicardial fat area (EFA) measurements on chest LDCT for prediction of MetS.

A total of 130 (mean age, 50.2±10.77 years) asymptomatic male who underwent nonelectrocardiography (ECG)-gated LDCT were divided into 2 groups for the main analysis (n=75) and validation (n=55). Each group was further divided into subgroups with or without MetS. EFV and EFA were calculated semi-automatically using commercially available software with manual assistance. The area under the curve (AUC) on receiver operating characteristic (ROC) analysis and cutoff values to predict MetS on LDCT were then calculated and validated. Female data were not available for analysis due to small sample size in this self-referred lung cancer screening program.

In the analysis group, the mean EFV was 123.12±42.29 and 67.30±20.68 cm\textsuperscript{3} for the MetS and non-MetS subgroups, respectively (P<.001), and the mean EFA was 7.95±3.10 and 4.04±1.73 cm\textsuperscript{2}, respectively (P<.001). Using 93.65 and 4.94 as the cutoffs for EFV and EFA, respectively, the sensitivity, specificity, positive and negative predictive values, and accuracy for predicting MetS were 84.2% and 84.2%, and 92.9% and 64.3% (P<.001); 80% and 44.4% (P=.01); 94.5% and 92.3%; and 90.7% and 69.3% (P<.001), respectively. The AUC for EFV and EFA for predicting MetS was 0.909 and 0.808 (95% confidence interval, 0.819–1.00 and 0.702–0.914, respectively) (P=.02). Using the same cutoff values in the analysis group, there was no significant difference in diagnostic performance using EFV and EFA between the analysis and validation sets.

Although quantification of both EFA and EFV is feasible on non-ECG-gated LDCT, EFV may be used to reliably predict MetS with fairly high and better diagnostic performance in selected population.

Abbreviations: AUC = area under the curve, DBP = diastolic blood pressure, EFA = epicardial fat area, EFV= epicardial fat volume, HDL = high-density lipoprotein, LDCT = low-dose computed tomography, MetS = metabolic syndrome, SBP = systolic blood pressure, TG = triglyceride.

Keywords: computed tomography, epicardial fat, low-dose computed tomography, metabolic syndrome

1. Introduction

Regional accumulation of visceral fat, particularly intraabdominal fat, may contribute to unfavorable cardiovascular events and metabolic risk factors.\textsuperscript{[1–5]} Epicardial fat is a local visceral fat deposit located between the myocardial surface and the visceral pericardium, and shares many of the pathophysiologic properties of abdominal fat deposits.\textsuperscript{[6]} Although epicardial fat is correlated with intraabdominal visceral fat, and both affect atherogenesis, intraabdominal fat produces a more systemic effect in promoting insulin resistance, and thus plays a key role in the development of metabolic syndrome (MetS).\textsuperscript{[7,8]} However, epicardial fat exerts a more localized paracrine effect on the coronary arteries and heart, through local production and release of inflammatory cytokines into the coronary circulation.\textsuperscript{[1,2,5–13]} Thus, the discovery that epicardial fat may have a direct influence on coronary atherosclerosis has increased interest in its use for prediction of adverse cardiac events.\textsuperscript{[9,10]} In contrast to intra-abdominal visceral fat, however, the pathogenetic role of epicardial fat in the development of atherosclerotic cardiovascu-
lar diseases and MetS has been less well documented,\textsuperscript{114–16} although epicardial fat was shown to be correlated with anthropometric and imaging measurements of visceral fat.\textsuperscript{117}

The increasing interest in quantification of epicardial fat has led to the adoption of noninvasive imaging techniques. Quantification by multidetector computed tomography (CT) was reported to be one of the most reliable and reproducible methods for estimating the extent of epicardial fat with high spatial resolution, although echocardiography and magnetic resonance imaging (MRI) have also been used.\textsuperscript{2,6,18} Traditionally, to minimize motion artifacts during CT scans and more accurately depict the thin pericardium, electrocardiography (ECG) synchronization has been used for quantification of epicardial fat during cardiac CT scanning, both for coronary calcium scoring and coronary angiography. Promisingly, however, a recent report showed that epicardial fat can also be quantified by nongated low-dose computed tomography (LDCT) of the chest, with results similar to those achieved using cardiac CT in ECG-gated acquisition mode.\textsuperscript{119} LDCT refers to a noncontrast CT study obtained with significantly less radiation exposure than is required for diagnostic chest CT.\textsuperscript{2,20} The use of LDCT for lung cancer screening has increased significantly based on promising reports from the National Lung Screening Trial in the United States. These reports indicated that LDCT screening reduces lung cancer-specific mortality by 20\% in high-risk individuals, compared with chest radiographic screening.\textsuperscript{21,22} However, only 24.2\% were positive and most (95\%) of the lesions found on positive screens were benign.\textsuperscript{22} In cases not associated with lung cancer, we hypothesized that LDCT screening may provide additional benefits by screening for other conditions, such as MetS, through measurement of epicardial fat burden, which is also included in the scanning range in this risk-sharing population. We also hypothesized that 3-dimensional (3D) quantification of epicardial fat would be better correlated with MetS than 2-dimensional (2D) measurements. For this purpose, we performed volume measurements and compared the results using a 2D metric to determine whether MetS could be predicted more accurately with application of 3D volumetric measurement.

The present study was performed to assess the feasibility of quantification of epicardial fat area (EFA) and epicardial fat volume (EFV) on LDCT, and then to investigate the potential of these measurements for reliable prediction of MetS. Our approach was based on determination of threshold values to compare the diagnostic performance of EFA and EFV via a cross-validation strategy.

2. Materials and methods

2.1. Study population

We retrospectively included 130 consecutive healthy male subjects who underwent non-ECG-gated LDCT for lung cancer screening and measurement of anthropometric and biochemical parameters, as part of a basic medical checkup on the same day between January 2015 and March 2015. No exclusion criteria applied in this study. The subjects were randomly divided into 2 groups for the main analysis (n = 75, analysis set) and a validation study (n = 55, validation set). Data from the latter group were used only to validate the proposed cutoff value for diagnosis of MetS. Each group was then divided into 2 subgroups (with or without MetS) based on the International Diabetes Federation (IDF) criteria. The components of MetS are central obesity (waist circumference ≥90 cm for Asian males) plus any 2 of the following four additional factors: triglyceride (TG) level ≥150 mg/dL; high-density lipoprotein (HDL) cholesterol <40 mg/dL; systolic blood pressure (SBP) ≥130 or diastolic blood pressure (DBP) ≥85 mm Hg, or treatment of previously diagnosed hypertension; and fasting plasma glucose ≥100 mg/dL or previously diagnosed type 2 diabetes.\textsuperscript{16} This study was approved by our institutional review board and the requirement for informed consent was waived (IRB no: 2014-10-027-001).

2.2. Measurement of anthropometric and biochemical parameters

Waist circumference, SBP, and DBP were measured during the subject’s visit. TG, HDL cholesterol, and fasting plasma glucose levels were also measured during their visit after an at-least a 12-hour fast.

2.3. Low-dose chest CT

All subjects had undergone non-ECG-gated chest CT on a 64-slice multidetector CT system (Discovery CT 750 HD; GE Healthcare, Milwaukee, WI). Image acquisition parameters were 64 × 0.625 mm section collimation, 500 milliseconds rotation time, 120 kVp tube voltage, 35 mAs tube current, and a reconstructed section thickness of 2 or 3 mm. All CT studies were available in standard Digital Imaging and Communications in Medicine (DICOM) format and were analyzed offline using a standalone workstation with dedicated image processing software.

2.4. Quantification of epicardial fat

Epicardial fat includes all adipose tissue surrounded by the visceral pericardium, which is detected as a thin line on CT. The EFV and EFA were semiautomatically calculated using commercially available postprocessing software (Aquarius; TeraRecon, San Mateo, CA) with manual assistance for identifying fat voxels and defining the pericardial border (Fig. 1). For measurement of EFV, the pericardium was manually traced at 5 or 6 slices from its superior extent (bifurcation of the pulmonary trunk) to the inferior end of the pericardial sac (the last slice containing the heart).\textsuperscript{117} The software then generated pericardial contours between the user-defined pericardial linings. These automatically traced pericardial contours were manually adjusted as necessary. The EFA was determined at the mid-ventricular level in the axial plane, by measuring the epicardial volume of a slice divided by the slice thickness. A threshold of −190 to −30 Hounsfield units (HU) was applied to extract the fat-containing voxels for quantification of both EFV and EFA.\textsuperscript{12,13} All image sets were anonymized and presented randomly. A cardiac radiologist with 10 years of experience then measured the EFV and EFA in all subjects in both the analysis and validation sets. One month later, 2nd and 3rd volume and area measurements were performed by the same investigator, to determine intraobserver variability in a subset of 25 patients randomly selected from the analysis set. In addition, a 2nd experienced reader independently performed the measurements to determine interobserver variability in these patients.

2.5. Statistical analysis

Statistical analyses were performed using SPSS (IBM Corp, Released 2017, IBM SPSS Statistics for windows, Version 25.0;
IBM Corp, Armonk, NY) and R software (ver 3.1.3; R Foundation for Statistical Computing, Vienna, Austria). A 2-tailed P-value < .05 was taken to indicate statistical significance. The general characteristics of the study groups are summarized as counts and percentages for qualitative variables and means ± standard deviation (SD) for quantitative variables. To compare EFV and EFA performance, each was described using receiver operating characteristic (ROC) analyses. The area under the curve (AUC) and the 95% confidence interval (CI) of this area were then used to assess the ability to predict the presence of MetS. Based on the AUC statistic, the AUC was defined as poorly predictive (0.5 ≤ AUC < 0.7), moderately predictive (0.7 ≤ AUC < 0.9), or highly predictive (0.9 ≤ AUC < 1).[23] Delong method was used to compute the 95% CI and P-values for the AUCs of EFV and EFA. The optimal EFV and EFA for predicting MetS were determined by Youden index. The sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) for the optimal cutoffs were then calculated. To assess the performance of the optimal cutoffs, those of the EFV and EFA were applied to the validation set for prediction of MetS, after which their diagnostic performance was evaluated. Inter- and intraobserver reliabilities of the EFV and EFA measurements were evaluated based on the intraclass correlation coefficient (ICC).

3. Results

3.1. Patient characteristics in analysis set
Measurements were performed successfully in all subjects. The analysis set consisted of 75 subjects with a mean age (±SD) of 50.2 ± 10.77 years (range: 23–74 years). Among them, the MetS subgroup consisted of 19 subjects with a mean age of 49.21 ± 13.68 years. The characteristics and measurements of the analysis set are provided in Table 1. There were no significant differences in mean age, SBP, or DBP between the non-MetS and MetS subgroups. However, the 2 groups showed significant differences in mean waist circumference, mean plasma levels of TG and HDL, and fasting blood glucose (all P < .05). The EFV was markedly higher in the MetS subgroup than the non-MetS subgroup (123.12 ± 42.29 vs 67.30 ± 20.68, respectively, P < .001). Patients with MetS had significantly greater EFA than those in the non-MetS subgroup (7.95 ± 3.10 vs 4.04 ± 1.73, respectively, P < .001).

3.2. Diagnostic performance of epicardial fat measurements
Using a cutoff value for EFV of 93.65, its sensitivity, specificity, PPV, NPV, and accuracy for predicting MetS were 84.2%, 92.9%, 80%, 94.5%, and 90.7%, respectively. Using 4.94 as the
the ICC in a randomly selected subset of 25 subjects. The EFV
Intraobserver and interobserver agreements were evaluated using

3.4. Interobserver and intraobserver variability

measurements showed excellent intraobserver and interobserver reproducibility (ICC: 0.99, 95% CI: 0.977–0.993; and ICC: 0.985, 95% CI: 0.967–0.994, respectively), whereas EFA measurements showed excellent intraobserver reproducibility but only moderate interobserver reproducibility (ICC: 0.945, 95% CI: 0.875–0.976; and ICC: 0.765, 95% CI: 0.466–0.896, respectively).

4. Discussion

Our results indicated that quantification of epicardial fat is feasible on nongated LDCT, and that EFV is superior to EFA for prediction of MetS, with fairly high diagnostic performance. These results were consistent with those of previous investigations indicating that nongated LDCT examination allowed more reliable quantification of EFV than dedicated ECG-gated cardiac CT acquisition,\[^{[19]}\] while higher reproducibility was obtained with volumetric measurements than with distance measurements.\[^{[22]}\]

In the present study, both EFV and EFA were significantly higher in the MetS subgroup than the non-MetS subgroup of the analysis set. The diagnostic performance of epicardial measurements for prediction of MetS indicated a relationship of epicardial fat with MetS. As expected, however, MetS was more accurately predicted by EFV (P < .001) than by EFA in the analysis group. We hypothesized that EFV would be a better indicator of MetS because the accumulation of epicardial fat may be more accurately demonstrated using 3D volumetric measurements. Furthermore, epicardial fat is distributed unevenly among different patients. Thus, CT volumetric quantification may provide a more reliable result based on the amount of epicardial fat than on the thickness of the fat around the right cusp.

cutoff value for EFA, the sensitivity, specificity, PPV, NPV, and accuracy for predicting MetS were 84.2%, 63.4%, 44.4%, 92.3%, and 69.3%, respectively (Table 2). The use of EFV was associated with significantly higher specificity, PPV, and diagnostic accuracy for predicting MetS than EFA (all P < .05). The overall accuracy of EFV ≥ 93.65 for predicting MetS was high, with an AUC of 0.909 (95% CI: 0.819–1.000), whereas EFA ≥ 4.94 had a moderate AUC of 0.808 (95% CI: 0.702–0.914) (P < .05 for all measures; Delong method). Comparison of the AUC values indicated that EFA was more accurate than EFV for predicting MetS (P = .02) (Fig. 2).

3.3. Validation study

Measurements were performed successfully in all subjects. There was no significant difference in the prevalence of MetS between subjects in the analysis and validation sets (Table 3). The mean EFV and EFA in the validation set did not differ significantly from the values in the analysis set (P = .22 and P = .92, respectively). The same EFV and EFA cutoff values were applied to the validation set for prediction of MetS in the validation set (Table 4). The diagnostic performance of EFV and EFA did not differ significantly between the analysis and validation sets (Table 5).

3.4. Interobserver and intraobserver variability

Intraobserver and interobserver agreements were evaluated using the ICC in a randomly selected subset of 25 subjects. The EFV

| Sample | Cutoff | Sensitivity | Specificity | Accuracy | PPV | NPV | AUC (95% CI) |
|--------|--------|-------------|-------------|----------|-----|-----|-------------|
| EFV, cm\(^3\) | 93.65 | 16/19 | (84.2%, 73.7–100%) | (92.9%, 80.4–98.2%) | (90.7%, 80–97.3%) | (80.8%, 58.3–94.7%) | (94.5%, 90.6–100%) | 0.909 |
| EFA, cm\(^2\) | 4.94 | 16/19 | (84.2%, 57.9–94.7%) | (64.3%, 55.4–94.6%) | (69.3%, 62.7–88%) | (44.4%, 37.8–80%) | (92.3%, 85–97.6%) | 0.808 |
| Comparison | | 1 | 20/56 | <.001 | <.001 | 0.01 | 0.69 | \(0.702–0.914\) | \(0.2\) |

Thresholds were derived by closest top left and Youden index. 95% Confidence intervals (CIs) were calculated using bootstrapping method. AUC = area under the curve, EFV = epicardial fat volume, NPV = negative predictive value, PPV = positive predictive value, THR = threshold.

\(^{[1]}\) P-values were computed by McNemar test for sensitivity, specificity, and accuracy. Fisher exact test for PPV and NPV; Delong method for AUC.
Figure 2. Receiver-operating characteristic curve to predict the presence of metabolic syndrome (MetS) using epicardial fat volume (EFV) and endocardial fat area (EFA) in the analysis group. The overall accuracy of EFV for predicting metabolic syndrome (MetS) was high with an area under the curve (AUC) of 0.909, whereas EFA had a moderate AUC of 0.808. Comparison of the AUC values indicated that EFV predicted MetS more accurately ($P < .05$) than EFA.

Table 3
Characteristics of the participants in the analysis and validation groups.

| Variable                  | Analysis set ($N=75$) | Validation set ($N=55$) | Comparison ($P$-value) |
|---------------------------|-----------------------|--------------------------|------------------------|
| Age                       | 50.2±10.77            | 52.53±10.54              | .51                    |
| No. of MetS               | 19 (25.3%)            | 13 (23.6%)               | .99                    |
| Epicardial fat volume, cm$^3$ | 81.70±37.04          | 90.41±41.33              | .22                    |
| Epicardial fat area, cm$^2$   | 5.48±2.80             | 6.12±4.95                | .92                    |

Data for epicardial fat measurements were presented as mean±standard deviation. MetS=metabolic syndrome. $^1P$-values were computed by Chi-squared test for categorical variable and Mann–Whitney U test for continuous variables.
Epicardial fat area, cm²  
EFA, cm² 4.94 11/13 24/42 35/55 11/29 24/26 0.728

Consistent with these standard CT with ECG gating has proven to be the most reliable agreement. Our results from the analysis set were then applied to the validation set for prediction of MetS, the diagnostic performance of EFV and EFA did not differ significantly between the 2 groups (Table 5). Our results demonstrated the correlation between epicardial fat and MetS, and thus the potential of EFV derived from screening LDCT for predicting MetS, by providing additional information about the epicardial fat burden. Furthermore, with an extra few minutes and a few additional mouse clicks, EFV data can be integrated into image analysis to allow the detection of MetS in patients undergoing chest CT for unrelated reasons.

Table 4:
Diagnostic performance of the epicardial fat measurement in the validation set using the cutoff value derived from the analysis set.

| Variable | Cutoff | Sensitivity | Specificity | Accuracy (CCR) | PPV | NPV | AUC (95% CI) |
|----------|--------|-------------|-------------|----------------|-----|-----|--------------|
| EFV, cm³ | 93.65  | 12/13       | 32/42       | 44/55          | 12/22 | 32/33 | 0.889        |
|          |        | 92.3% (46.7–99.6%) | 76.2% (61.5–86.5%) | 80.0% (67.6–88.4%) | 54.5% (45.5–92.3%) | 96.7% (90–100%) | 0.775–0.958 |
| EFA, cm² | 4.94   | 11/13       | 24/42       | 35/55          | 11/29 | 24/26 | 0.728        |
|          |        | 84.6% (57.8–95.7%) | 57.1% (42.2–70.9%) | 63.6% (50.4–75.1%) | 37.9% (31–87.5%) | 92.3% (82.9–100%) | 0.591–0.839 |

Comparison (P-value*)

95% Confidence intervals (CI) were calculated using bootstrapping method. Sensitivity, specificity, and CCR in the validation set are based on application of the cutpoint derived from the training set. CCR=correct classification rate, EFA=epicardial fat area, EFV=epicardial fat volume, PPV=positive predictive value, NPV=negative predictive value.

*P-values were computed by McNemar test for sensitivity, specificity, and accuracy. Fisher exact test for PPV and NPV.

ventricle, as is generally acquired in 2D echocardiography. Accordingly, to date, volumetric quantification using standard CT with ECG gating has proven to be the most reliable and reproducible method to evaluate the amount of epicardial fat.

Consistent with these findings, our results demonstrated that the volumetric approach is more accurate and more reproducible than the area measurement, even using non-ECG-gated LDCT. Our results also confirmed that nongated LDCT examination may be sufficient for delineation of pericardial contours and that EFV measurements on LDCT are easily reproducible, with excellent interobserver and intraobserver agreement.

Our results from the analysis set were then validated in an independent group, and the cutoff values of EFV and EFA were well matched between the 2 groups. Furthermore, when the cutoff values calculated from the analysis set were applied to the validation set for prediction of MetS, the diagnostic performance of EFV and EFA did not differ significantly between the 2 groups (Table 5).

Our findings demonstrated the correlation between epicardial fat and MetS, and thus the potential of EFV derived from screening LDCT for predicting MetS, by providing additional information about the epicardial fat burden. Furthermore, with an extra few minutes and a few additional mouse clicks, EFV data can be integrated into image analysis to allow the detection of MetS in patients undergoing chest CT for unrelated reasons.

We acknowledge several limitations of our study. First, the potential of EFV derived from screening LDCT for predicting MetS, by providing additional information about the epicardial fat burden. Furthermore, with an extra few minutes and a few additional mouse clicks, EFV data can be integrated into image analysis to allow the detection of MetS in patients undergoing chest CT for unrelated reasons.

We acknowledge several limitations of our study. First, the potential of EFV derived from screening LDCT for predicting MetS, by providing additional information about the epicardial fat burden. Furthermore, with an extra few minutes and a few additional mouse clicks, EFV data can be integrated into image analysis to allow the detection of MetS in patients undergoing chest CT for unrelated reasons.

Second, the number of patients with MetS included in this study was relatively small. As described earlier, however, LDCT was performed on asymptomatic, healthy individuals for lung cancer screening and evaluation of possible pulmonary abnormalities. This may explain the low rate of MetS in our study population. Further validation of the results should be performed in larger MetS populations. Next, we did not evaluate the effects of acquisition protocols on quantification of epicardial fat. CT scans using different kVp and mA tube parameters may alter the EFA and cutoff values; nonetheless, our data suggested that LDCT protocols may allow the best cutoff values for prediction of MetS with fairly high accuracy. Finally, differences in MetS definitions may cause discrepancies in the results. However, their impact on using epicardial fat to predict MetS was not evaluated in this study. MetS is a clustering of cardiovascular risk factors including at least 3 of the following clinical conditions: central obesity, males referred for lung cancer screening.

Since diagnostic criteria for MetS have gender-specific cutoff values, small sample size restricted a meaningful analysis of statistical significance in the female group of the present study, which may be due to low smoking prevalence among Asian females. Although this may limit the generalization of the study findings, we chose the study population considering the male predominance in the lung cancer screening program at our institution, and the complexity of the analysis due to gender and ethnic differences in MetS criteria. Nevertheless, our results support further validation studies for females and other ethnic groups. Second, the number of patients with MetS included in this study was relatively small. As described earlier, however, LDCT was performed on asymptomatic, healthy individuals for lung cancer screening and evaluation of possible pulmonary abnormalities. This may explain the low rate of MetS in our study population. Further validation of the results should be performed in larger MetS populations. Next, we did not evaluate the effects of acquisition protocols on quantification of epicardial fat. CT scans using different kVp and mA tube parameters may alter the EFA and cutoff values; nonetheless, our data suggested that LDCT protocols may allow the best cutoff values for prediction of MetS with fairly high accuracy. Finally, differences in MetS definitions may cause discrepancies in the results. However, their impact on using epicardial fat to predict MetS was not evaluated in this study. MetS is a clustering of cardiovascular risk factors including at least 3 of the following clinical conditions: central obesity,
elevated fasting plasma glucose, elevated blood pressure, high serum TGs, and low high-density lipoprotein levels. Among the various criteria with different cutoff points for similar components, which have been used since 1998 for clinical diagnosis of MetS, we applied the IDF guidelines in our ethnically homogeneous study population, based on their ethnicity-specific values for central obesity.\textsuperscript{[16]}

In conclusion, the quantification of epicardial fat was feasible on nongated LDCT, with EFV proving superior to EFA for prediction of MetS. These results suggest a correlation between epicardial fat and MetS, and thus demonstrate the potential for quantifying EFV on screening LDCT to predict MetS with fairly high diagnostic accuracy.

**Author contributions**

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**Formal analysis:** Heon Lee, Bora Lee.

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