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Prediction of Coronary Artery Calcium Using Deep Learning of Echocardiograms

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SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.echo.2022.12.014.

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Abstract

Background: Coronary artery calcification (CAC), often assessed by computed tomography (CT), is a powerful marker of coronary artery disease that can guide preventive therapies. Computed tomographies, however, are not always accessible or serially obtainable. It remains unclear whether other widespread tests such as transthoracic echocardiograms (TTEs) can be used to predict CAC.

Methods: Using a data set of 2,881 TTE videos paired with coronary calcium CTs, we trained a video-based artificial intelligence convolutional neural network to predict CAC scores from parasternal long-axis views. We evaluated the model's ability to classify patients from a held-out sample as well as an external site sample into zero CAC and high CAC (CAC ≥ 400 Agatston units) groups by receiver operating characteristic and precision-recall curves. We also investigated whether such classifications prognosticated significant differences in 1-year mortality rates by the log-rank test of Kaplan-Meier curves.

Results: Transthoracic echocardiogram artificial intelligence models had high discriminatory abilities in predicting zero CAC (receiver operating characteristic area under the curve [AUC] = 0.81 [95% CI, 0.74–0.88], F1 score = 0.95) and high CAC (AUC = 0.74 [0.68–0.8], F1 score = 0.74). This performance was confirmed in an external test data set of 92 TTEs (AUC = 0.75 [0.65–0.85], F1 score = 0.77; and AUC = 0.85 [0.76–0.93], F1 score = 0.59, respectively). Risk stratification by TTE-predicted CAC performed similarly to CT CAC scores in prognosticating significant differences in 1-year survival in high-CAC patients (CT CAC ≥ 400 vs CT CAC < 400, P = .03; TTE-predicted CAC ≥ 400 vs TTE-predicted CAC < 400, *P* = .02).

Conclusions: A video-based deep learning model successfully used TTE videos to predict zero CAC and high CAC with high accuracy. Transthoracic echocardiography–predicted CAC prognosticated differences in 1-year survival similar to CT CAC. Deep learning of TTEs holds promise for future adjunctive coronary artery disease risk stratification to guide preventive therapies.

Keywords

Coronary artery calcium; Echocardiogram; Deep learning; Machine learning; Convolutional neural network

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Coronary artery calcification (CAC) is a highly specific marker of atherosclerosis that is the result of pathogenic inflammatory, metabolic, and developmental processes.[1] Assessment of CAC now plays an increasingly important role in risk stratification for coronary artery disease (CAD) and prognostication in asymptomatic patients. Guidelines from both the American College of Cardiology/ American Heart Association and European Society of Cardiology endorse using CAC scores for guiding decisions on the use of lipidlowering therapy and aspirin as well as informing discussions around modification of cardiovascular risk factors.[2,3] Individuals with no coronary calcium have an extremely low risk of

cardiovascular disease and mortality over the next 15 years and may safely deescalate certain medical therapies.4,5 Conversely, individuals with any coronary calcium have a greater risk of long-term cardiovascular events and mortality that increases with the amount of calcium and represents risk beyond those predicted by traditional clinical risk factors.[6–8]

Although CAC is visualizable by multiple x-ray-based imaging modalities including chest radiography and fluoroscopy, CAC is most frequently assessed by the Agatston scoring method using computed tomography (CT) imaging.[9] Despite the potential usefulness of information gained from CAC CTs, concerns remain about patient exposure to ionizing radiation, inappropriate use of testing, cost, and an increase in the detection of incidental noncardiac findings.[10–13] In light of these considerations, at least 1 guideline body, the U.S. Preventive Task Force, concluded in 2018 that there was insufficient evidence to formally recommend CAC for cardiovascular risk stratification.[14] These limitations have also tempered the use of serial CAC CTs for ongoing disease surveillance, even though the rate of CAC progression is known to provide additional prognostic insight.[7,,15]

Recent advances in computational techniques have revealed that machine learning when applied to information-dense medical images can identify disease phenotypes and prognosticate outcomes beyond what is possible by expert clinician observation alone.[16–19] Given that some clinicians and patients may remain apprehensive about or may not have easy access to CAC CTs, we sought to understand whether applying deep learning to other widely used cardiovascular tests, such as transthoracic echocardiograms (TTEs), could leverage already acquired imaging to complement and extend the prognostic power of CAC assessment.

In this retrospective study of patients with both CAC CTs and TTE studies, we used a video-based deep learning architecture to predict (1) the presence of any CAC and (2) the presence of high CAC levels (CAC score ≥ 400) from standard TTE views. In addition to validating results in an external test data set, we tested whether these model predictions could be used to successfully prognosticate differences in 1-year mortality and applied model attribution methods to better understand areas of focus by the deep learning model.

METHODS

Dataset

We identified all patients with CT studies with CAC scoring performed at Cedars-Sinai Medical Center, a large multisite urban health system, from January 1, 2015, to December 31, 2020, who also had a TTE completed within 1 year of the CAC study. While a CAC score could be paired with potentially multiple TTEs, each TTE could only be paired with a single CAC score. Using multiple studies to predict a single label has been established as a helpful method that can improve the performance of deep learning models.[17]

Per institutional protocol, CAC scoring was performed on chest CTs with noncontrast image volumes according to standard imaging acquisition and Agatston scoring methods.[9] Computed tomography scans were acquired using Siemens and GE CT scanners. Echocardiograms were acquired using Philips EPIQ 7 or iE33 ultrasound machines.

Echocardiogram characteristics (left ventricular ejection fraction (LVEF), presence of wall motion abnormalities, and presence of at least moderate valvular disease) were obtained from echocardiogram reports. To better characterize our cohort, we distinguished echocardiograms with "≥moderate valvular disease" as any TTE with moderate or worse regurgitant or stenotic disease in any of the 4 heart valves.

For deep learning, each TTE study was initially sourced in Digital Imaging and Communications in Medicine format and contained multiple video loops and still images. Videos corresponding to the standard parasternal long-axis (PLAX) view were extracted, masked, and down-sampled by cubic interpolation to a resolution of 112 × 112 pixels per previously described methods.[16] The PLAX view was chosen because it visualizes anatomical features adjacent to the proximal coronary arteries that can experience early calcification (i.e., the aorta and aortic valve), is readily identified by automated view classifiers, and is easily obtainable by even novice ultrasound scanners.[20,21] We randomly split our data set using 80% of TTEs for model training, 10% for model validation, and 10% for hold-out testing. For a supplemental analysis, we also extracted apical 4-chamber (A4C) views from the same TTEs. Since some studies did not have both highquality PLAX and A4C views, the number of PLAX and A4C videos was different.

We obtained an additional limited external data set from Stanford Healthcare containing all TTEs completed within 1 year of CAC studies performed from July 1, 2016, to August 1, 2018. The A4C and PLAX videos were extracted from these TTEs and then masked and down-sampled according to a workflow similar to what was used for processing TTEs from Cedars-Sinai.

This study was approved by the Institutional Review Boards at Cedars-Sinai Medical Center and Stanford Healthcare.

Assessment of Patient Characteristics and Outcomes

Patient characteristics were derived from electronic health records data according to standard Elixhauser comorbidity definitions.[22] The atherosclerotic cardiovascular disease (ASCVD) risk score for 10-year risk of heart disease or stroke was calculated for a subgroup of 402 patients who had available cholesterol and blood pressure information.[23] Mortality information was sourced from deaths recorded in the electronic health records as well as from the California Department of Public Health Death Index.

Deep Learning Model Selection and Training

We trained a convolutional neural network model with residual connection and spatiotemporal convolutions across frames to predict CAC scores. This model, based on the R2+1D architecture, has been previously used successfully to predict LVEF from TTEs.[16] Our model was initialized with pretrained weights from the EchoNet-Dynamic data set.[16] The model was trained to minimize the squared loss between the prediction and log (CAC score + 1) using an Adam optimizer with a learning rate of 0.001 and batch size of 10 across 40 epochs.

The model input used video clips of 32 frames, which were created by sampling every other frame. The weights from the epoch with the lowest validation loss were used for final model testing on the held-out data set. Model training was done in Python using the publicly available PyTorch deep learning library.

Model Performance and Survival Analysis

We evaluated the ability of our model to correctly classify patients into coronary calcium versus no coronary calcium groups as well as CAC score ≥ 400 versus <400 groups. We tested our model on the held-out test set and an external test set from Stanford Healthcare, as well as a subset of the original held-out data set containing only patients ages <70 years old. We displayed receiver operating characteristic (ROC) and precision-recall (PR) curves to demonstrate model performance across classification thresholds. As a measure of overall model performance, we reported the area under the curve (AUC) for the ROC and PR curves as well as F1 scores. Confidence intervals were reported using 10,000 bootstrapped samples.

To compare our model's performance with the prognostic abilities of a CAC score of zero by CT, we used predicted calcium scores to stratify patients into low or high risk using the score cutoff that was most accurate for predicting the presence of CAC (highest mean of sensitivity and specificity). We then also divided these same patients into low or high risk based on whether they had a CAC score of 0 or >0 by CT. We then determined whether there were significant differences in mortality rates between these groups by the log-rank test of Kaplan-Meier curves over a 1-year period from the date of the TTE or CT. The same process was repeated when comparing the TTE model's performance with the predictive abilities of a CAC score of ≥200 and ≥400 by CT. Lastly, we calculated net reclassification indices for 1-year mortality when going from risk stratification by CT CAC score of 0 to risk stratification by TTE-predicted CAC score of 0.[24]

Survival analysis was conducted using R software (ver. 3.4.1) survival and survminer packages.

Model Interpretability

We attempted to visualize the input features that were most influential in our deep learning models using the integrated gradients attribution method, which has several advantages over other attribution methods including its ability to better meet the tests of sensitivity and implementation invariance.[25] We chose representative output images using this attribution method on PLAX models.

RESULTS

We trained a CNN model on a dataset of 2,881 TTEs paired with coronary calcium scores from 1,635 patients. Patients had a mean age of 72 years (SD = 14.3), were 37.4% female and 31.4% nonwhite, and had a range of cardiovascular comorbidities (25.4% hypertension, 36.9% heart failure, 59.8% hyperlipidemia; Table 1). Patients with available cholesterol and blood pressure information were on average at intermediate cardiovascular risk, with a mean ASCVD risk score of 13.6% (SD = 11.4%). Over three quarters of patients had a normal LVEF, and 69.2% of echocardiograms had no wall motion abnormalities. The mean

absolute difference in time between TTE and CT was 68.6 days (SD = 96.0), with 13.4% having a calcium score of 0 and 53.0% having a calcium score ≥400. An external dataset from Stanford Healthcare contained 92 TTEs paired with coronary calcium scores from 92 patients. The mean patient age was 58.4 years (SD = 11.7), and 43.4% were female. Almost all TTEs had a normal LVEF, with 47.8% of TTEs paired with a calcium score of 0 and 17.4% with a calcium score ≥400.

When tested on a held-out dataset not used for model training, the CNN model had high discriminatory abilities in predicting which patients had 0 calcium (ROC AUC = 0.81 [95% CI, 0.74–0.88], F1 score = 0.95; Figure 1A). The model performed modestly well in predicting patients who had high calcium scores >400 Agatston units (AUC = 0.74 [0.68–0.8], F1 score = 0.74; Figure 1B) and intermediate calcium scores >200 Agatston units (AUC = 0.75 [0.69–0.81], F1 score = 0.78; Supplemental Figure 1). On the external data set of TTEs from Stanford Healthcare, the model was able to again predict patients who had zero coronary calcium (AUC = 0.75 [0.65–0.85], F1 score = 0.77) as well as those with high coronary calcium (AUC = 0.85 [0.76–0.93], F1 score = 0.59; Figure 2).

In supplemental analyses, we found that a model trained using A4C videos was able to also predict both zero CAC (AUC = 0.73 [0.67–0.79], F1 score = 0.95) and high CAC (AUC = 0.72 [0.68–0.76], F1 score = 0.73; Supplemental Figure 2). However, performance was worse compared to the model using PLAX videos, especially when applied to the external data set (AUC = 0.55 [0.47–0.64], F1 score = 0.67 for zero CAC; AUC = 0.73 [0.62–0.84], F1 score = 0.33 for CAC > 400).

Since our patient cohort was on average older than the typical target population for CAC screening, we performed an additional sensitivity analysis by testing our model in a limited subset of patients younger than 70 years old who were not used in model training. This subset had a mean age of 57.7 years (SD = 9.8) and mean ASCVD risk score of 10.1% (SD = 9.2%), with 22% of patients having a calcium score of 0 (Supplemental Table 1). Prediction performance was similar when compared to testing in the entire cohort of patients in predicting zero coronary calcium (AUC = 0.79 [0.73–0.85], F1 score = 0.87) and high coronary calcium (AUC = 0.74 [0.67–0.81], F1 score = 0.64; Supplemental Figure 3).

We compared the risk discrimination abilities of our TTE CAC prediction model to having a CT CAC score of 0 in predicting 1-year survival. Both risk stratification by TTE-predicted CAC and CT CAC produced survival curves that separated by 1 year, although in both cases, the separation was not statistically significant, likely because the sample size was underpowered to detect a significant difference (CT calcium vs CT no calcium, $P = .20$; TTE-predicted calcium vs TTE-predicted no calcium, $P = .07$; Figure 3A). When comparing survival curves in patients with a TTE-predicted CAC score >400 or a CT CAC >400, both methods of CAC assessment were in fact able to significantly predict 1-year survival (Figure 3B). When going from a CT CAC score of 0 to a TTE-predicted CAC score of 0, there was an improved net reclassification index for nonevents (=0.12 for PLAX) and similar net reclassification index for events (=−0.04 for PLAX; Supplemental Table 2).

In an exploratory interpretability analysis using the integrated gradients attribution method, we found that the model appeared to focus more heavily on the aortic valve anulus, aorta, left ventricular outflow tract, and mitral valve (Figure 4).

DISCUSSION

Assessing the risk of CAD in asymptomatic individuals continues to be a cornerstone for ensuring that patients receive appropriate preventive care and therapies. Echocardiography is a widely available, noninvasive, and radiation-free diagnostic tool that captures a large amount of physiological information that could be used for helping better assess CAD risk. In this retrospective study of patients with both CAC and TTE studies, we demonstrated for the first time that a video-based deep learning algorithm using standard TTE views successfully predicted with high accuracy whether individuals had developed CAC as well as high levels of coronary calcium. These predictions additionally stratified patients into risk groups that performed similarly in predicting 1-year mortality when compared to CAC scores by CT.

With the application of machine learning techniques, it has become increasingly clear that diagnostics such as TTEs and electrocardiograms contain patterns of information that can be used for predicting patient characteristics and disease states beyond what may be immediately discernible by the human expert.[17–19,21] In this study, we showed that deep learning of TTEs successfully predicted the presence of any CAC as well as high levels of calcium. Using TTE images to predict the presence of CAC, as opposed to another endpoint such as hard cardiovascular events, for example, is particularly valuable because the development of CAC is an early upstream process that may identify a key time window during which preventative therapies may be most effective. Indeed, there already exists a robust body of evidence linking the detection of CAC to actionable therapies such as the use of aspirin and statins.[2,3]

The connection between TTE images and CAC has a compelling physiological basis that warrants further investigation. Cardiac structural changes that are visualizable in the PLAX view, such as systolic and diastolic ventricular dysfunction, aortic and mitral valve calcification, and aorta calcification, are well known to be associated with CAD.[26–29] Deep learning of PLAX views has been able to predict aortic stenosis with high accuracy.[30] Attribution methods confirmed that our deep learning algorithm appeared to focus on the aorta, left ventricular outflow tract, and aortic and mitral valves. We further propose that PLAX videos may have performed better in predicting CAC than A4C videos because PLAX views best visualized calcification of the aorta and aortic valve.

We confirmed that the calcium predictions by TTE deep learning models appeared to stratify patients into risk groups that had 1-year all-cause mortality rates similar to those predicted using CT CAC scores. In fact, we even observed a slight improvement in net reclassification of nonevents, meaning that patients who were deemed high risk by CT CAC were correctly reclassified into the low-risk group when using TTE-predicted CAC instead. As a result, in contrast to the TTE-predicted CAC survival curves, there was no statistical difference seen for the CT calcium versus CT no calcium curves at 1 year given the lower difference

in mortality rates between the 2 groups. The reason for this improved performance using TTE-predicted CAC is not immediately clear and remains to be confirmed in larger studies with greater power to detect differences in survival. It could be that there are additional features present in a TTE video that may help distinguish when a subset of patients with CAC are lower risk for future adverse events. It is known, for example, that statins, while reducing future cardiovascular events, can accelerate CAC, meaning that calcification in certain patients may not in fact be as worrisome.[31]

If confirmed in subsequent prospective testing, the use of deep learning of TTEs for CAD risk stratification could have several potentially intriguing applications. While we do not anticipate echocardiograms replacing CAC CTs, given the widespread availability of TTEs, deep learning of TTEs could conceivably be used for CAC approximation when CAC scoring by CT is deferred by the patient or inaccessible. There also may be a role for using these models to help patients and clinicians decide whether to pursue a CAC CT if the decision is unclear. When CAC scores by CT are obtained, such models could act as an adjunct to inform the interpretation of CAC scores to give an overall more accurate picture of disease. Transthoracic echocardiograms could also have a potential role in serial monitoring for the development of CAD years after a 0 CAC score. Prediction of high CAC scores may have additional uses such as determining when coronary CT angiography might have an increased likelihood of being nondiagnostic due to the presence of high calcium levels.

Several study limitations warrant consideration. Transthoracic echocardiogram and CAC assessment were not performed simultaneously, although we ensured that they occurred within 1 year of each other with the mean absolute difference in time being slightly over 2 months. We included all recorded CAC scores that could be paired with TTEs. However, our study population was on average older and had a high proportion of positive CAC scores, which is likely due to the older population that is seen at our institution and differences in local practice patterns, including the possibility that some CTs with CAC were ordered for other indications in addition to CAC assessment. Although all included TTEs and CT scans were ordered by referring clinicians for standard indications, we could not confirm whether patients had anginal symptoms at the time of their imaging test. The training cohort may therefore not be fully representative of the population for whom CAC scoring is most often used. Nevertheless, in the subgroup of patients with available cholesterol and blood pressure information, the mean ASCVD risk score fell within the intermediate cardiovascular risk range. Model performance remained similar when limiting the test data set to only patients <70 years old. The model was additionally able to perform well in an external data set of younger patients who had a much lower proportion of CT scans with positive CAC. We used all-cause death as our main outcome given its adjudication certainty, although cardiovascular-related outcomes would be more specific to CAD. While survival curves based on TTE-predicted CAC diverged at 1 year, longer-term follow-up in larger prospective studies properly powered to distinguish survival differences would be informative.

CONCLUSION

A video-based deep learning model successfully used TTE videos to predict the presence of CAC as well as high levels of coronary calcium with a high degree of accuracy. Coronary artery calcium predictions were additionally able to successfully prognosticate differences in 1-year mortality. These results speak to the potential role of using deep learning of TTEs for future CAD risk stratification to guide preventive therapies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

A4C	Apical 4 chamber
AI	Artificial intelligence
ASCVD	Atherosclerotic cardiovascular disease
AUC	Area under the curve
CAC	Coronary artery calcification, calcium
CAD	Coronary artery disease
CT	Computed tomography
LVEF	Left ventricular ejection fraction
PLAX	Parasternal long axis
PR	Precision-recall
ROC	Receiver operating characteristic
TTE	Transthoracic echocardiogram

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HIGHLIGHTS

- CAC is a powerful marker of CAD and can guide preventive therapies.
- We used 2,881 TTEs paired with CAC scores to train an AI CAC prediction model.
- The TTE-based deep learning model accurately predicted zero CAC and high CAC scores.
- This was confirmed in an external data set of 92 TTEs paired with CAC scores.
- CAC prediction by TTE AI performed similarly to CT CAC in predicting 1-year survival.

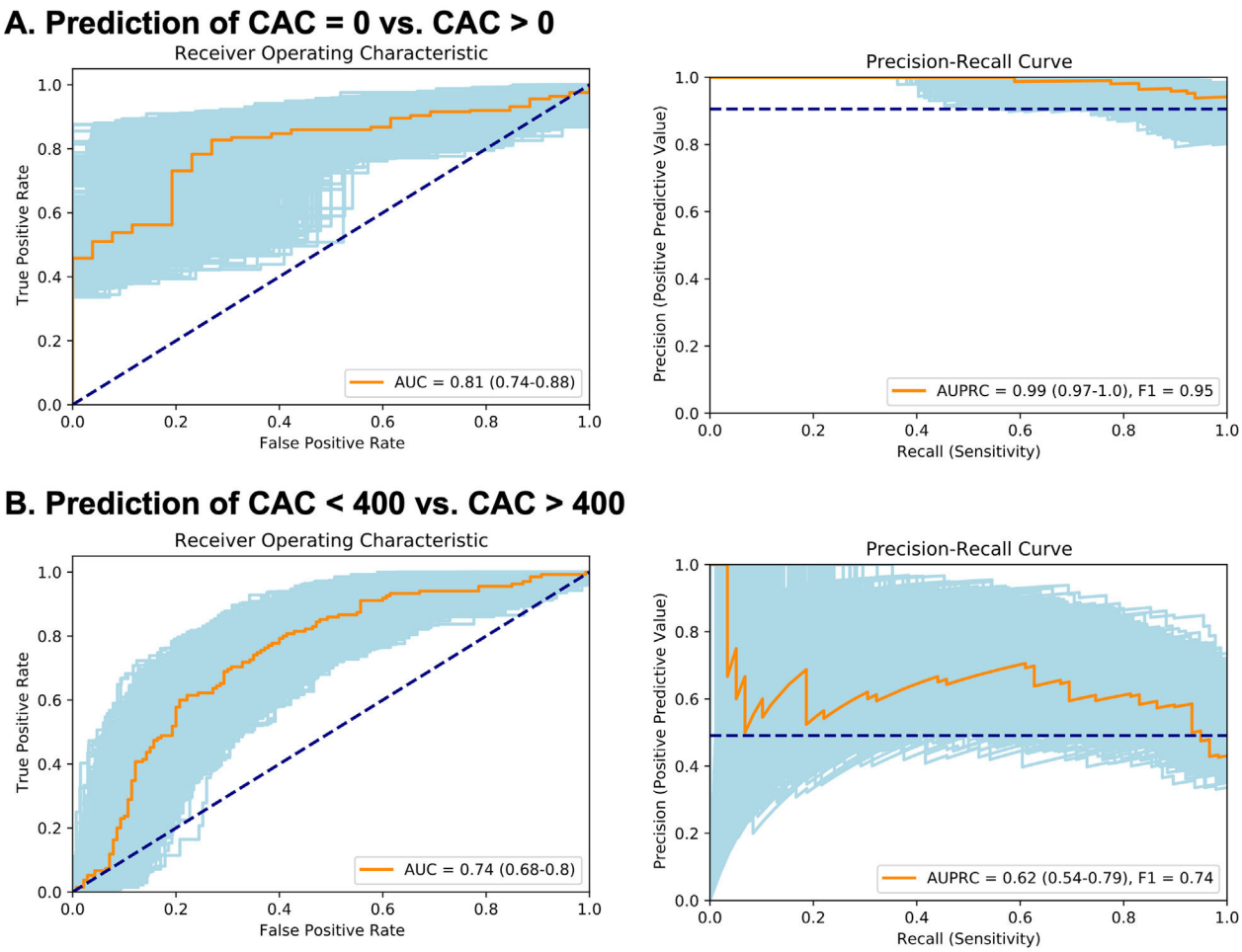

Figure 1.

Performance characteristics of a deep learning model for predicting CAC using PLAX TTE videos when applied to a held-out test data set. Receiver operating characteristic and PR curves across different classification thresholds with AUC (95% CI) and F1 score for predicting **(A)** presence versus absence of CAC and **(B)** CAC score < 400 versus >400 Agatston units.

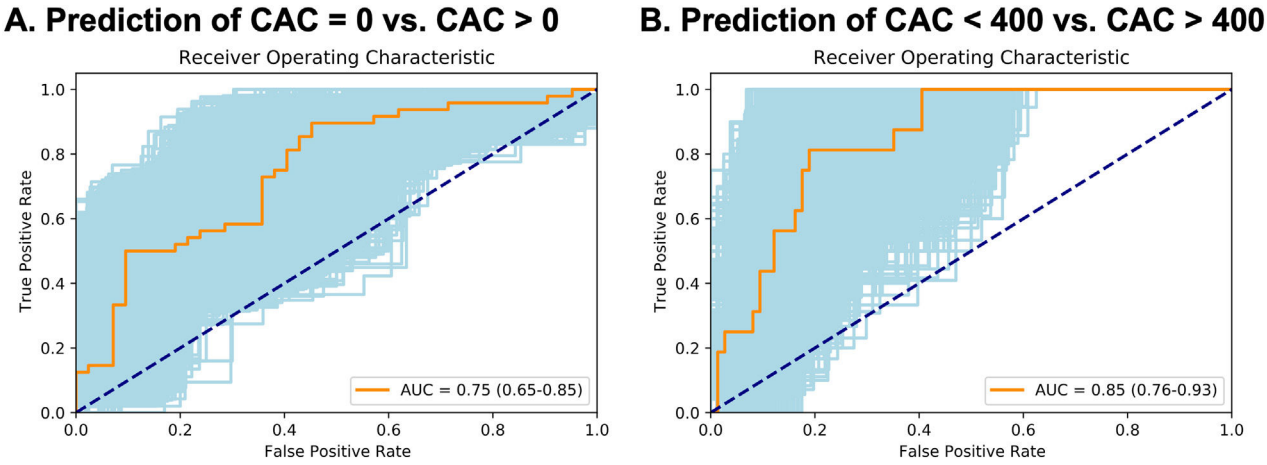

Figure 2.

Performance characteristics of a deep learning model for predicting CAC using PLAX TTE videos when applied to an external site test data set. Receiver operating characteristic and PR curves across different classification thresholds with AUC (95% CI) and F1 score for predicting **(A)** presence versus absence of CAC and **(B)** CAC score < 400 versus >400 Agatston units.

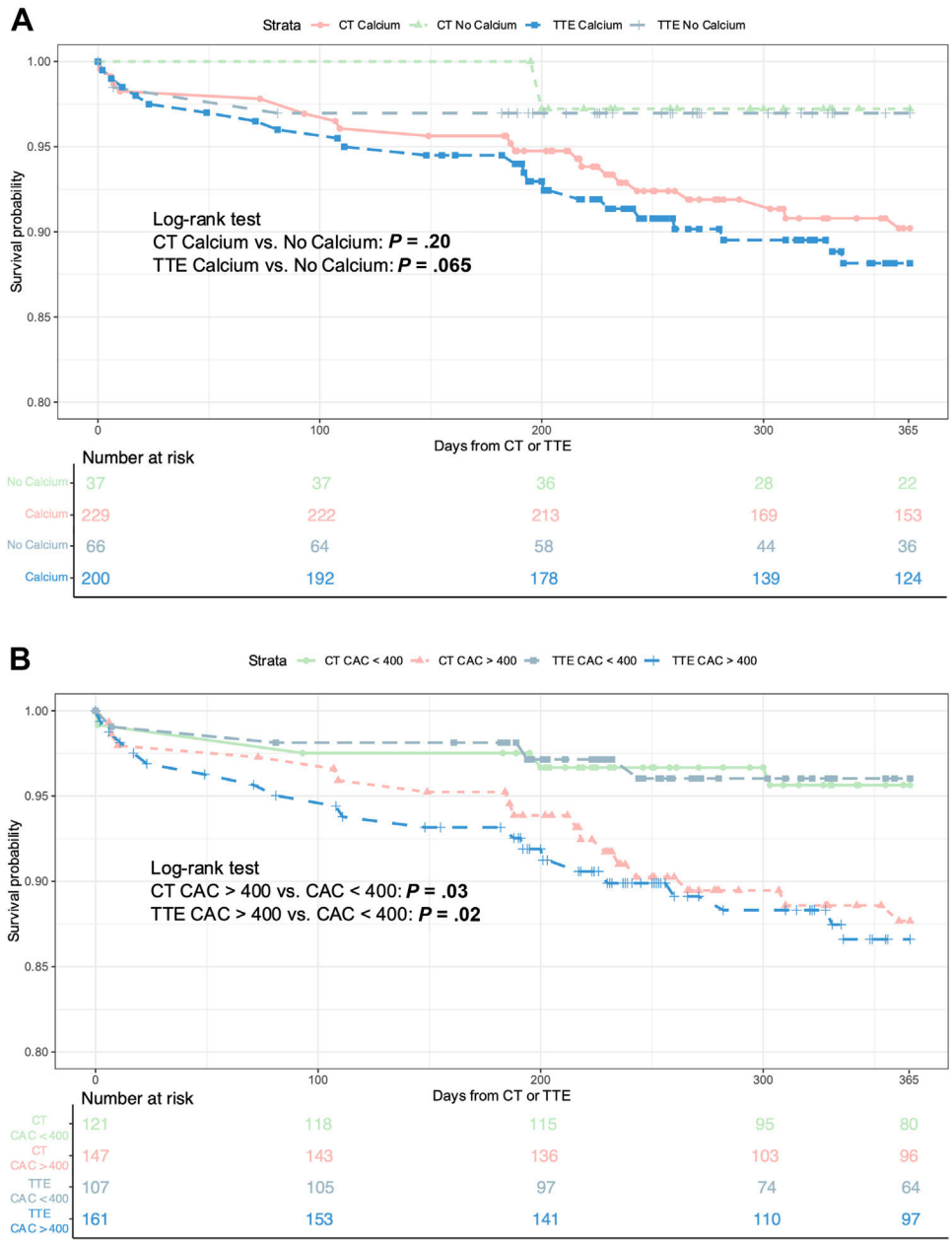

Figure 3.

Kaplan-Meier survival curves for all-cause mortality over 1 year for patients in a held-out test data set stratified by **(A)** CT CAC score 0 versus >0 or by TTE-predicted CAC score 0 versus >0 and **(B)** CT CAC score < 400 versus >400 or by TTE-predicted CAC score < 400 versus >400.

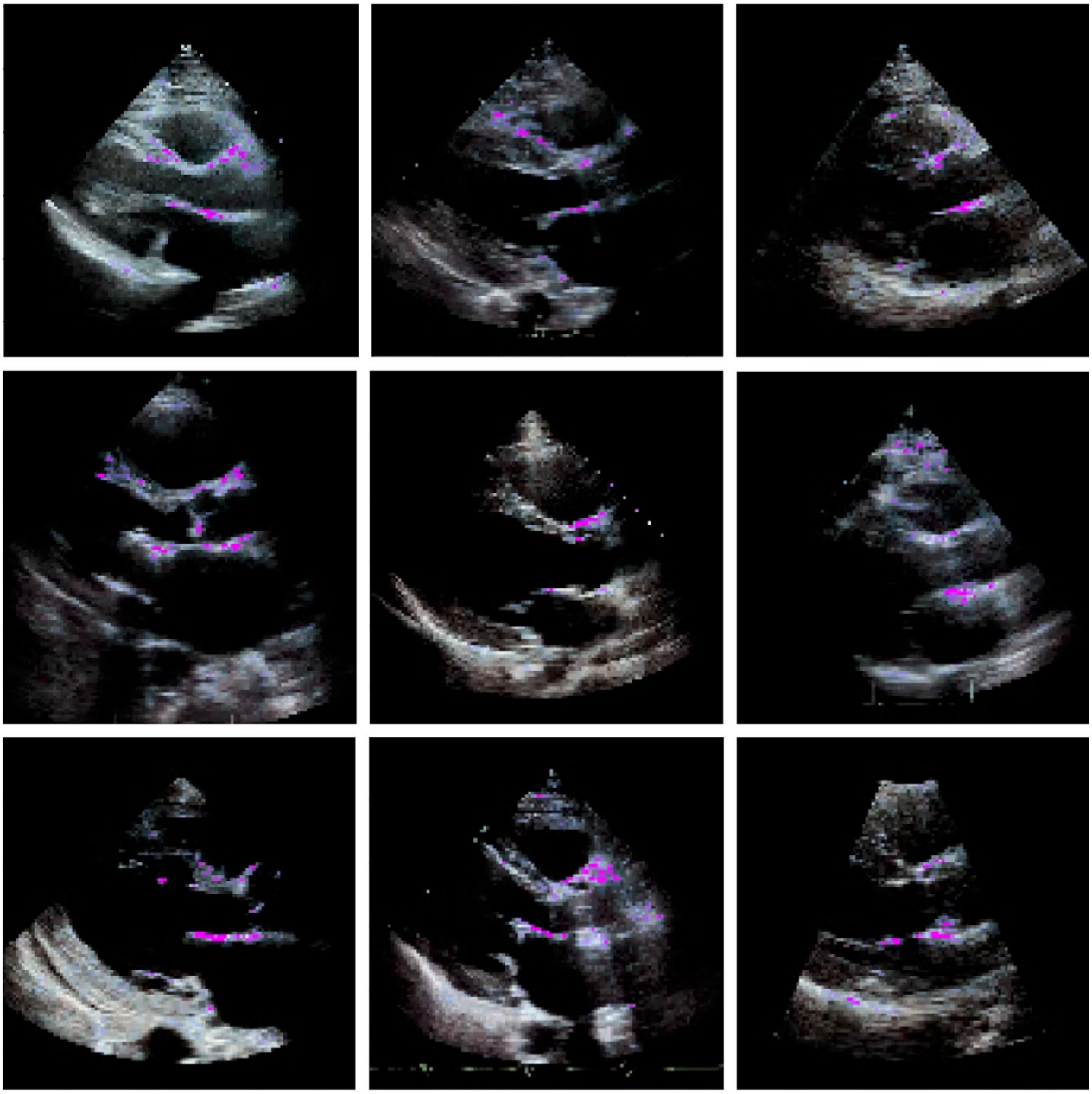

Figure 4.
Areas of focus by the deep learning model (*bright pixels*) according to results from the integrated gradients attribution method.

Table 1

Baseline patient, echo, and calcium score characteristics

Patients (*N* = 1,635)	
Age, mean (SD)	71.9 (14.3)
Gender, female	612 (37.4)
Race/ethnicity	
American Indian	5 (0.3)
Asian	101 (6.2)
Black	143 (8.7)
Hispanic	119 (7.3)
Non-Hispanic White	1,121 (68.6)
Other	129 (7.9)
Unknown	17 (1.0)
Hypertension	416 (25.4)
Heart failure	603 (36.9)
Hyperlipidemia	977 (59.8)
Diabetes	345 (21.1)
Obesity	116 (7.1)
Chronic lung disease	622 (38.0)
Chronic kidney disease	287 (17.6)
Active smoker	36 (2.2)
On hypertension medication	817 (50)
ASCVD risk score *	13.6 (11.4)
Echocardiogram videos paired with CAC (*N* = 2,881)	
Normal LVEF	2,166 (75.2)
Wall motion abnormality	886 (30.8)
≥Moderate valvular disease	569 (19.8)
Days from TTE to CT, mean (SD)	68.6 (96.0)
CAC = 0	385 (13.4)
CAC = 0–99	518 (18.0)
CAC = 100–399	450 (15.6)
CAC > 400	1,528 (53.0)
External site echocardiogram videos (*n* = 92)	
Age, mean (SD)	58.4 (11.7)
Gender, female	40 (43.4)
Normal LVEF	89 (96.7)
≥Moderate valvular disease	5 (5.4)
Days from TTE to CT, mean (SD)	40 (169.9)
CAC = 0	44 (47.8)
CAC = 0–99	16 (17.4)
CAC = 100–399	16 (17.4)
CAC > 400	16 (17.4)

Data are presented as *n* (%) unless otherwise specified.

*ASCVD risk scores were calculable for a subset of 402 patients that had complete data.