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Qualitative coronary artery calcification scores and risk of all cause, COPD and pneumonia hospital admission in a large CT lung cancer screening cohort

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Abstract

Background: Patients at high-risk for lung cancer and qualified for CT lung cancer screening (CTLS) are at risk for numerous cardio-pulmonary comorbidities. We sought to examine if qualitatively assessed coronary artery calcifications (CAC) on CTLS exams could identify patients at increased risk for non-cardiovascular events such as all cause, COPD and pneumonia related hospitalization and to verify previously reported associations between CAC and mortality and cardiovascular events.

Study Design and Methods: Patients (n=4673) from Lahey Hospital and Medical Center who underwent CTLS from January 12, 2012 through September 30, 2017 were included with clinical follow-up through September 30, 2019. CTLS exams were qualitatively scored for the presence and severity of CAC at the time of exam interpretation using a four point scale: none, mild, moderate, and marked. Multivariable Cox regression models were used to evaluate the association between CT qualitative CAC and all-cause, COPD-related, and pneumonia-related hospital admissions.

Results: 3631 (78%) of individuals undergoing CTLS had some degree of CAC on their baseline exam: 1308 (28.0%), 1128 (24.1%), and 1,195 (25.6%) had mild, moderate and marked coronary calcification, respectively. Marked CAC was associated with all-cause hospital admission and pneumonia related admissions HR 1.48; 95% CI 1.23–1.78 and HR 2.19; 95% 1.30–3.71, respectively. Mild, moderate and marked CAC were associated with COPD-related admission HR 2.30; 95% CI 1.31–4.03, HR 2.17; 95% CI 1.20–3.91 and HR 2.27; 95% CI 1.24–4.15.

Conclusion: Qualitative CAC on CTLS exams identifies individuals at elevated risk for all cause, pneumonia and COPD-related hospital admissions.

INTRODUCTION

Coronary artery calcification (CAC) is a well-documented predictor of cardiovascular events, cardiovascular mortality and all-cause mortality.(1–3) Qualitative scoring of CAC in a computed tomographic lung cancer screening (CTLS) population has been shown to be comparable to Agatston CAC scoring and has been shown to be associated with cardiovascular events.(1–3) There are limited studies examining the risk of non-cardiovascular events, such as chronic obstructive pulmonary disease (COPD) and pneumonia related hospitalizations, in CLTS populations.(4–6)

In the United States, 14.5 million patients are estimated to be eligible for CTLS(7, 8). Patients who qualify for CTLS are high-risk patients often suffering from numerous cardio-pulmonary comorbidities making this group an ideal study population.(9) Using a large clinical CTLS cohort, we sought to examine the following primary and secondary endpoints. Primary endpoint: Utility of qualitatively assessed CAC to identify patients at increased risk for non-cardiovascular events such as all cause and COPD and pneumonia related hospitalization. Secondary endpoints: Confirm previously reports association between coronary calcification and mortality and cardiovascular events. Determine if there is a clinical opportunity to improve quality metrics: active smoking, blood pressure control and lipid management in patients with CAC identified on baseline CTLS exams.

METHODS

Subjects

This is a retrospective, single-center study of all patients, from Lahey Hospital and Medical Center (LHMC), Burlington, MA, who underwent CTLS from January 1, 2012 through September 30, 2017.(10, 11) All patients met the National Comprehensive Cancer Network (NCCN) Guidelines® Lung Cancer Screening Version 1.2012 high-risk criteria for lung cancer, Briefly, individuals eligible for lung cancer screening can be classified into NCCN group 1 and 2. This includes group 1) patients aged 55–74 years with ≥ 30 pack-year smoking history and smoking cessation <15 years or group 2) age ≥ 50 years and ≥ 20 pack year smoking history and 1 additional risk factor (other than 2nd hand smoke). All groups were pooled for the statistical analysis. All patients were asymptomatic and had a physician order for CTLS, were free of lung cancer for ≥ 5 years, and had no known metastatic disease, as previously described.(10–12)

Clinical Variables

Multiple clinical variables were collected prospectively as part of the CTLS program and stored in a centralized data repository. Additional clinical variables not already available in this data repository, including, last date of follow up, body mass index (BMI), race, mortality, cause of death, blood pressure, total cholesterol, low density lipoprotein (LDL), clinical scoring of emphysema and CAC were collected retrospectively by automated and manual review of the electronic medical record (EMR) and stored utilizing a custom-

designed database (FileMaker ProVersion 11; Filemaker Inc, Santa Clara, California). Clinical follow-up data was obtained through September 30th 2019. Hospital admissions were collected using Lahey administrative coding data. Principal admission diagnoses of COPD, pneumonia, congestive heart failure (CHF), acute myocardial infarction (AMI), and stroke were characterized based on diagnosis codes per 2018 Center for Medicare and Medicaid Services (CMS) condition-specific measures.(13)

Qualitative Emphysema and Coronary Calcium—Staff radiologists specifically trained in the interpretation of lung screening exams prospectively scored the degree of emphysema and coronary calcium qualitatively on all CTLS exams at the time of exam interpretation, using standardized ordinal categories of “none”, “mild”, “moderate”, and “marked”, as previously described.(1, 10)

CT scans

All CTLS examinations were performed on ≥64-row multidetector CT scanners (LightSpeed VCT and Discovery VCT [GE Medical Systems, Milwaukee, Wisconsin]; Somatom Definition [Siemens AG, Erlangen, Germany]; iCT [Philips Medical Systems, Andover, Massachusetts]) at 100 kV and 30 to 100 mA, depending on the scanner and the availability of iterative reconstruction software. Axial images were obtained at 1.25- to 1.5-mm thickness with 50% overlap and reconstructed with both soft tissue and lung kernels. Axial maximum-intensity projections (16 × 2.5 mm) and coronal and sagittal multiplanar reformatted images were reconstructed and used for interpretation.

Statistical Analysis

Cox proportional hazards regression was utilized to evaluate associations with primary and secondary outcomes of time to first all cause hospitalization, COPD, pneumonia, all-cause mortality, CHF, AMI and stroke related admissions. Variables known to be associated with risk of mortality all cause admission, COPD, pneumonia: age, sex, race, BMI, current smoking status, pack years of smoking, and emphysema severity were included in multivariable Cox proportional hazards models for each of the outcomes.(10, 14) In addition, NCCN group was included in the multivariable model to adjust for inherent confounding based on the baseline differences between these groups. CHF, AMI and stroke admission were adjusted for age, sex, race and pack years of smoking so not to overfit the models. Kaplan-Meier plots were generated to visualize the associations between observed baseline CAC and mortality; first all cause hospitalization; and first COPD, pneumonia, CHF, AMI and stroke related admissions. Chi-squared tests were used for inter group comparisons for differences between radiologist scoring of CAC and emphysema. Sensitivity analyses were performed adjusting for radiologist, and separately, the subset of patients who had Lahey PCPs. A subset analysis of quality metrics including blood pressure, total cholesterol and total LDL were extracted from the EMR were performed utilizing patient with in network PCP’s. Data was limited to in network PCP’s as our EMR does not have access to patients with out of network primary care physician’s routine blood pressure and lipid profiles. Data was expressed and total and % of patients meeting the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7) recommendation of a minimum goal BP <140/90(15) and the National Cholesterol

Education Program (NCEP) Adult Treatment Panel (ATP) III recommendation for treatment of total cholesterol >200 and LDL ≥130 mg/dL in patients with 2 or more cardiovascular risk factors.(16) To adjust for multiplicity Bonferroni correction was utilized for our three primary outcomes and p-value significance was set at <0.017. Otherwise, significance levels were set at a p-value < 0.05. All statistical analyses were performed using STATA14.1 software.

RESULTS

A total of 4,673 individuals underwent CTLS during the study period. The mean age was 62.4 ± 6.2 years, 2543 (54.4%) were male, 4,405 (94.3%) were white, 3,657 (78.3%) were NCCN Group 1, 2310 (49.4%) were former smokers with an average year quit of 10.0 ± 8.4, 2,666 (57.0%) had emphysema and 3,631 (77.7%) had evidence of CAC. Of these, 1308 (28.0%), 1128 (24.1%), and 1,195 (25.6%) had mild, moderate and marked coronary calcification, respectively. Table 1.

There was a similar distribution of CAC scoring among radiologists with three radiologists reading the vast majority 3915 (83.8%) of the scans. Radiologists reading less than 100 scans each were grouped together for this comparison as they read a combined total of only 143 (3.06%) scans, see Supplemental Table 1. There was a statistically significant difference between radiologist scoring of moderate and marked, P = <0.001 but there was no statistical difference between radiologists for none and mild CAC, P > 0.05.

There was a similar distribution of emphysema scoring among radiologists, as previously described.(10)

Primary Endpoints:

Qualitative CAC and All-cause hospital admission—There were 2,829 all-cause hospital admissions, of which 1,248 (26.7%) patients were admitted to the hospital at least once. The one year and two year hospital admission rates were 387 (8.3%) and 679 (14.5%), respectively.

On multivariable analysis the presence of marked CAC was associated with an increased risk for all-cause hospital admission, HR 1.48; 95% CI 1.23–1.78. Figure 1, shows the unadjusted Kaplan-Meier survival plot for extent of CAC and the probability of being free from all-cause admission over time, Table 2.

Qualitative CAC and COPD admission—Of the 4,673 participants, 150 (3.21%) were admitted for COPD at least once. On multivariable analysis mild, moderate and marked CAC (compared to no CAC) was associated with an increased risk of COPD admission , HR 2.30; 95% CI 1.31–4.03, HR 2.17; 95% CI 1.20–3.91 and HR 2.27; 95% CI 1.24–4.15, respectively, Table 2. Figure 2, shows a Kaplan-Meier survival plot for CAC severity and the probability of being free from COPD admission over time.

Qualitative CAC and Pneumonia admission—A total of 169 (3.61%) participants were admitted for pneumonia at least once. On multivariable analysis marked CAC was

associated with an increased risk of pneumonia admission, HR 2.19; 95% 1.30–3.71, Table 2, Figure 3 shows unadjusted Kaplan-Meier survival plot for CAC and the probability of being free from pneumonia admission over time.

Secondary Endpoints:

Qualitative CAC and Mortality—There were 273 (5.8%) deaths, of which 119 (43.6%) were other/unknown etiology, 70 (25.6%) secondary to cancer, 47 (17.2%) secondary to pulmonary etiology and 47 (17.2%) secondary to cardiovascular etiology.

On multivariable analysis the presence of marked CAC compared to no CAC was associated with an increased risk for mortality, HR 2.48; 95% CI 1.60–3.85, Table 3. Figure 4, shows unadjusted Kaplan-Meier survival plot for extent of CAC and the probability of being free from mortality over time.

Qualitative CAC and Cardiovascular admissions—A total of 73 (1.6%), 53 (1.1%) and 49 (1.0%) patients were admitted for CHF, AMI and stroke at least once.

On multivariable analysis moderate and marked were associated with increased risk of AMI admission, HR 4.81; 95% CI 1.61–14.34 and HR 3.66; 95% CI 1.17–11.52, respectively, Table 3. Figure 5 shows a Kaplan-Meier survival plot for CAC and the probability of being free from AMI admission over time.

On multivariable analysis moderated and marked CAC were associated with an increased risk for stroke, HR 3.62; 95% CI 1.00–13.03 and HR 5.45; 95% CI 1.53–19.39, Table 3. Figure 5, shows the Kaplan-Meier survival plot for CAC and the probability of being free from stroke admission over time.

Quality Metrics:

In a subset of patients with an in-network primary care physician, approximately 50% of patients with CAC identified on their baseline CTLS exams were actively smoking. Of these patients with mild, moderate and marked CAC on baseline CTLS exams, 58.6%, 60.3% and 76% of the patients had total cholesterol levels < 200 mg/dL, respectively. Approximately 80% of the patients with CAC on baseline exams had systolic blood pressures less than 140, Table 4. In a subset of active smokers with moderate CAC, 73.1% had a total cholesterol level <130mg/dL and 40.4% <100mg/dL. Of those with marked CAC, 85% had LDL cholesterol levels less than 130 mg/dL; and 59.6% had a total cholesterol < 100 mg/dL, Table 5.

DISCUSSION

The association between CAC and the risk for COPD and pneumonia admissions has not been well defined.(1–4) The association between COPD and coronary artery disease (CAD) is well documented and is thought to be due to inflammation.(17–19) Mota et al. demonstrated that the presence of COPD was associated with an increase in CAC independent of established risk factors for CAD.(6) In patients with COPD, CAC correlates with degree of functional impairment and mortality.(20) We have previously demonstrated

that qualitatively assessed emphysema is associated with risk for COPD hospitalization in two independent CTLS cohorts.(10) Our current study demonstrates that qualitative assessments of CAC are also associated with an increased risk for COPD and pneumonia admission independent of emphysema severity.

Our results confirm the previously reported association between CT CAC and risk of mortality and cardiovascular events.(1–3) The JNC 7 recommends a minimum goal BP <140/90 with lower treatment thresholds for patients with diabetes or chronic kidney disease.(15) The National Cholesterol Education Program (NCEP Adult Treatment Panel (ATP) III recommends treatment of LDL ≥130 mg/dL in patients with 2 or more cardiovascular risk factors.(16) Our data suggests there are opportunities to improve known cardiovascular risk factors such as smoking, lipid profiles and blood pressure management in our CTLS population. Fentanes et al demonstrated that preventative cardiology clinics focused on cardiovascular disease risk-management improved lipid and blood pressure management and treatment compliance. (21) In addition, clinic patients were more likely to be reclassified to higher risk categories with the use of CAC scores.(21)

As a single center study our results may not be generalizable other patient populations. In addition our study sample was predominantly white and lacked minority representation, which is a function of the location of our facility in a particular metropolitan suburb with relatively homogenous ethnicity. This lack of diversity may underestimate the effects of certain social determinants of health on CTLS outcomes. Our hospitalization data was only collected for those patients admitted within our hospital network. Hence, data about admissions of patients to hospitals outside our health systems may not have been captured. This may result in an underestimation of the true rates of hospitalization. However, in our sensitivity analysis excluding patients without in network primary care physicians the hazard ratios were similar (data not shown). Hospital admissions data were collected using Lahey administrative coding data to provide a principal diagnosis for each hospitalization thus the validity of each diagnosis may not be as rigorous as a detailed chart review. However, these metrics are the basis for how hospital systems are assessed and penalized for 30 day readmission metrics based on 2018 Center for Medicare and Medicaid Services (CMS) condition-specific measures.(13)

An additional limitation is that we did not account for the competing risk of death in our hospital admission models.

We also included both NCCN group 1 and group 2 in our study design. NCCN group 2 patients are younger with lower tobacco exposure. When the analysis was run separately for NCCN group 2 there was no significant difference in outcomes in our group 2 patients which had a significantly lower number of events (data not shown). Since our cohort is predominately NCCN group 1 these results are only generalizable to NCCN group 1 patients.

A limitation of our study is that it is standard practice for our radiologists to clinically score CAC and this data was utilized for our analysis. Our standard clinical scoring did not allow us to assess inter-rater reliability between radiologists for the scoring of degrees of CAC. We

did include scoring radiologist in the multivariable models and the results did not change (data not shown). Future studies utilizing automated quantitative methods to measure CAC may help address this limitation.

Future study is needed to see if quantitative CAC scores improves risk stratification. We did not have baseline hypertension treatment and diabetes status in our cohort and were unable to calculate an atherosclerotic cardiovascular disease risk score. A better characterization of cardiovascular risk profiles in CTLS populations would allow for a more accurate estimation of the potential for risk factor modification in this high risk population.

Patients who qualify for CTLS are at high-risk for numerous cardio-pulmonary comorbidities. The ability to identify patients at high risk for cardiovascular and pulmonary hospitalization, would enable health care institutions to implement programs that provide targeted clinical care for this subgroup of higher-risk patients. Interventions, such as COPD screening through pulmonary function testing (PFTs), intensive smoking cessation programs, vaccination against pneumococcal pneumonia, referral to a pulmonary specialist and dedicated clinics for cardiovascular risk reduction can potentially be implemented in CTLS populations and referral guided by qualitative or quantitative CAC and emphysema scores. These interventions have all been shown to reduce hospitalizations and improve outcomes in patients with COPD and cardiovascular risk factors.(10, 22–28)

As previously reported CAC and emphysema are common incidental findings on CTLS exams and have the potential to be both a qualitative and quantitative biomarker to help discriminate patients at risk for adverse events.(10, 29, 30) Further study is needed to determine if qualitative and quantitative CAC scoring can be incorporated in risk prediction models for cardiovascular and pulmonary related hospitalizations in CTLS populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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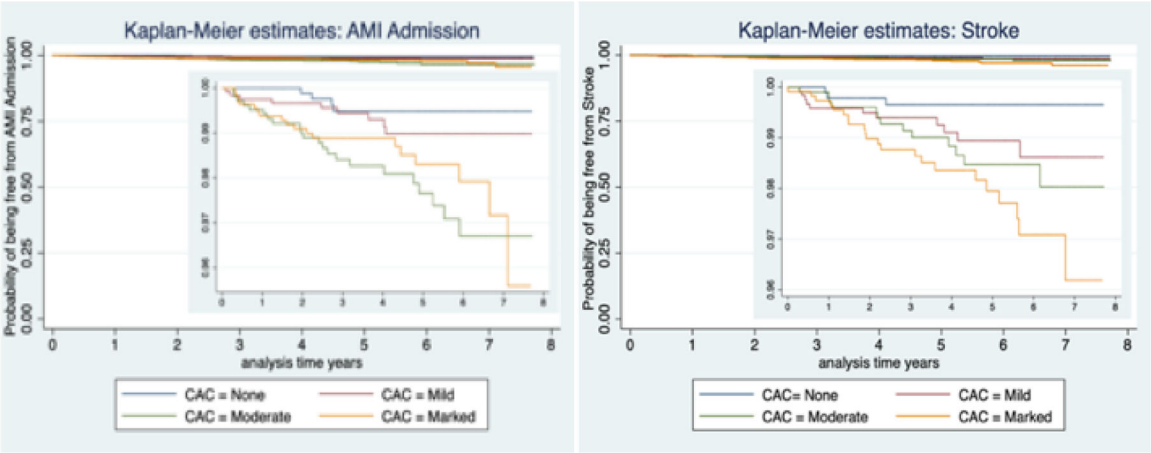

Figure 1:
Kaplan-Meier Plot for Coronary artery calcification extent and all cause hospital admission

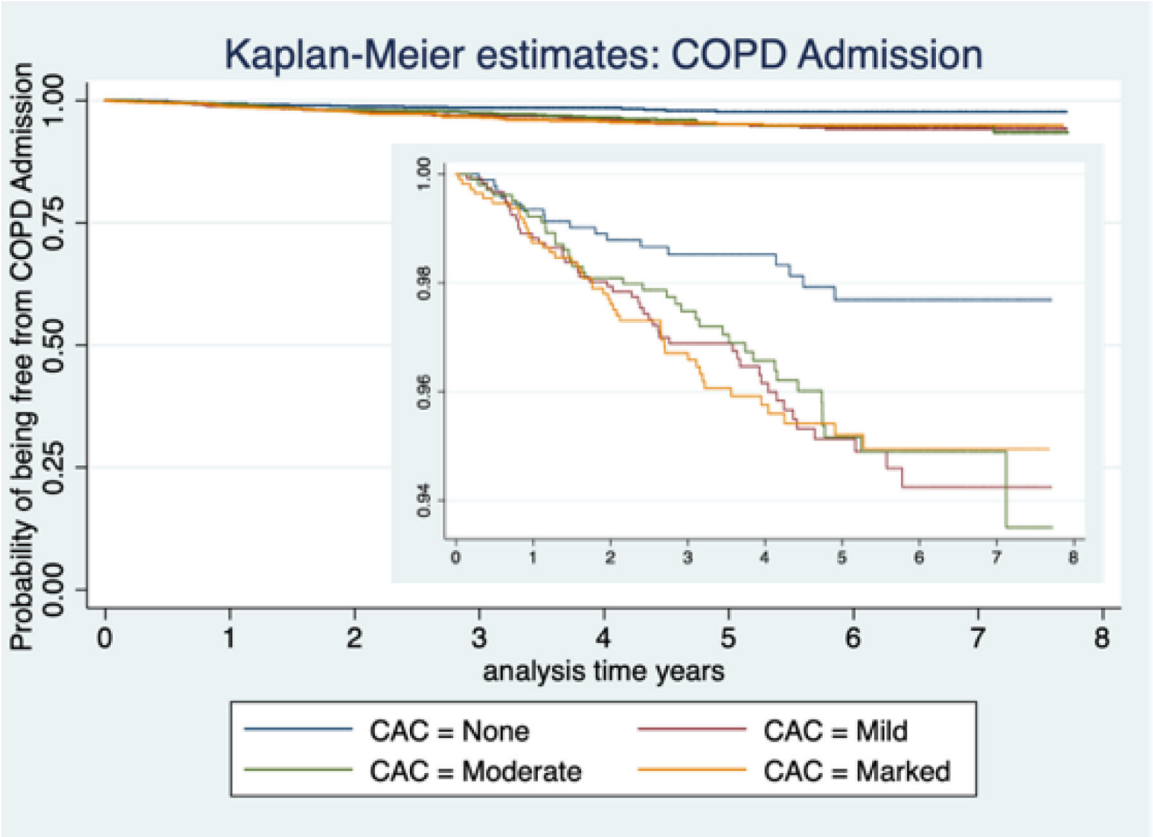

Figure 2:
Kaplan-Meier Plot for Coronary artery calcification extent and COPD related hospital admission

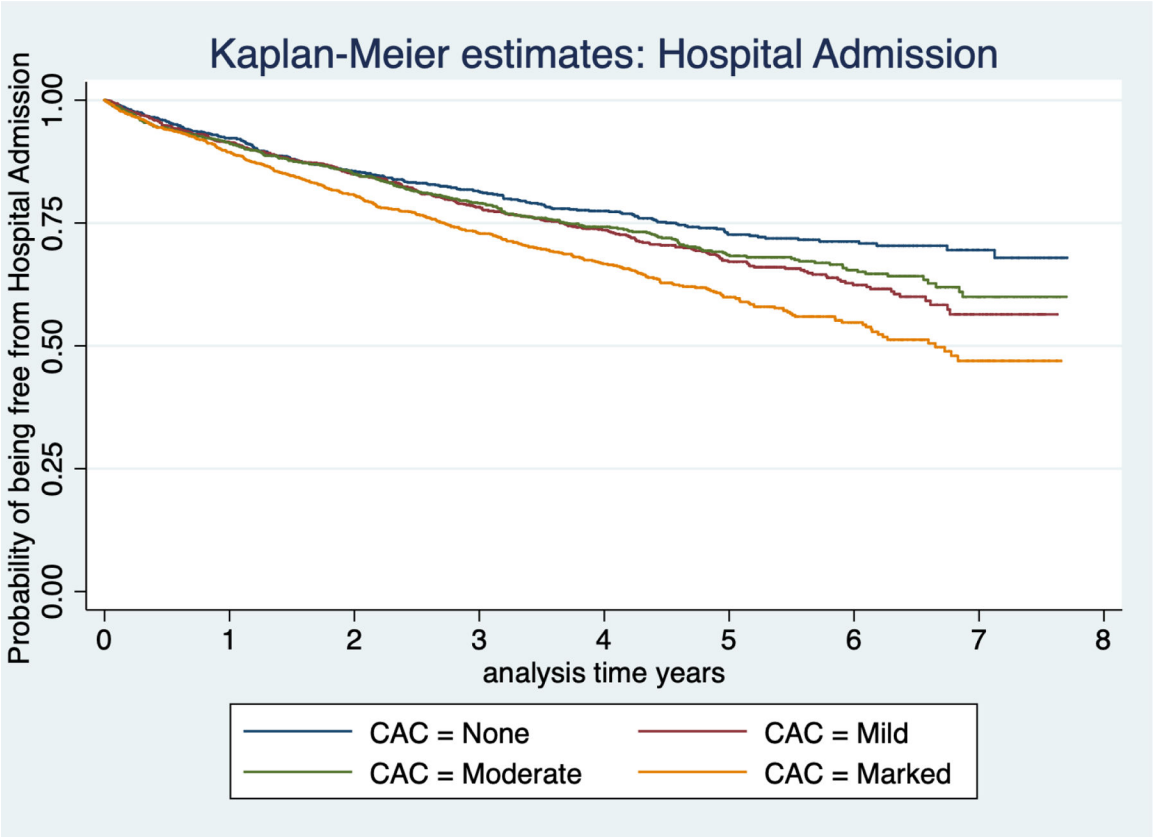

Figure 3:
Kaplan-Meier Plot for Coronary artery calcification extent and pneumonia related hospital admission

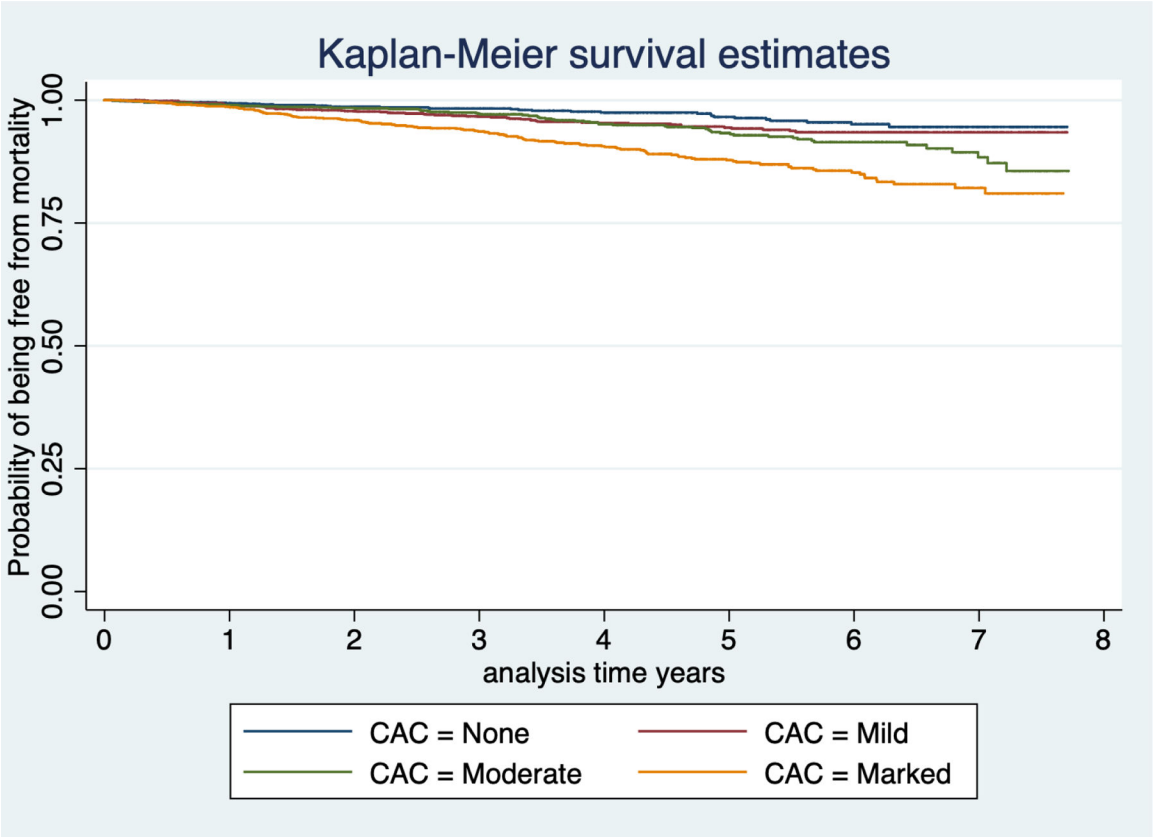

Figure 4:
Kaplan-Meier Plot for Coronary artery calcification extent and all-cause mortality

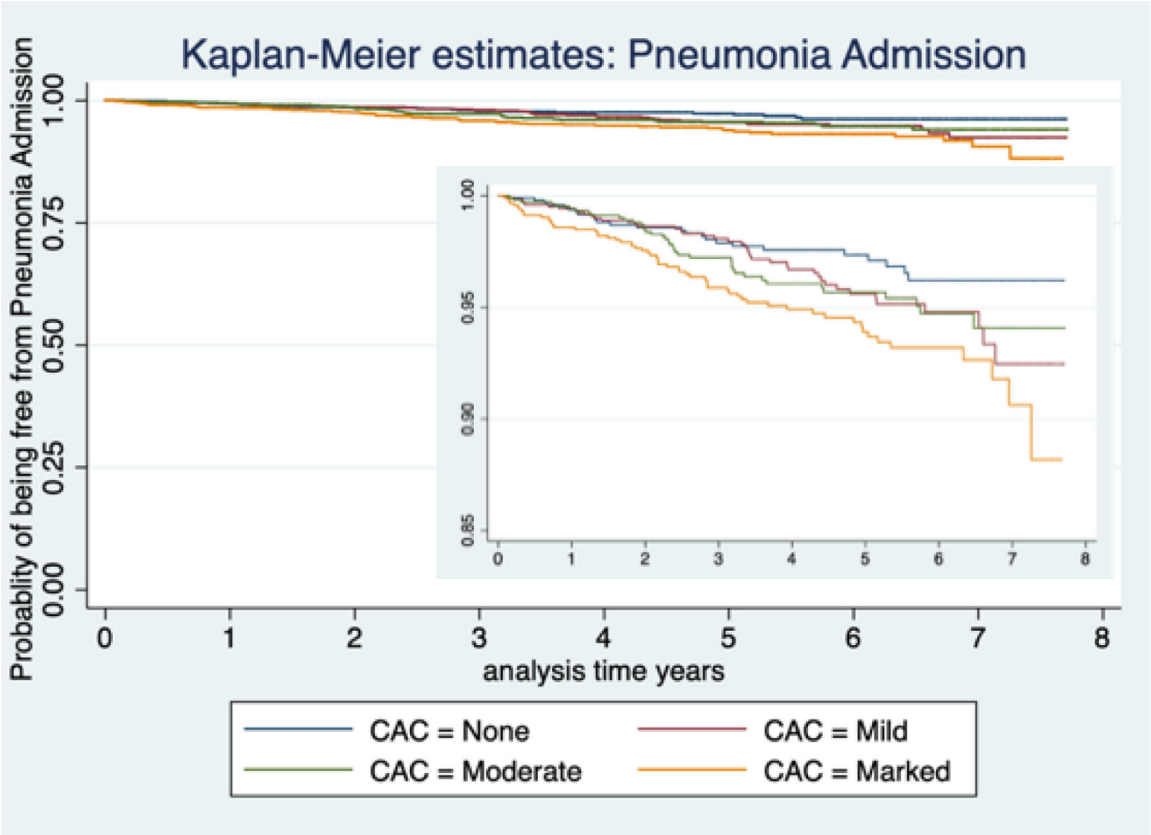

Figure 5:
Kaplan-Meier Plot for Coronary artery calcification extent and acute myocardial infarction and stroke related hospital admission

Table 1.

Demographics of CTLS Cohort.

	LHMC
	(N=4,673)
Age	62.4 ± 6.2
Sex:	
Male	2543 (54.4%)
Race:	
White Race	4405 (94.3%)
Asian	41 (0.9%)
African American	18 (0.4%)
Other	209 (4.5%)
BMI	29.2 ± 6.0
In Network PCP	3225 (69.0%)
Smoking:	
Current	2363 (50.6%)
Pack Years	48.6 ± 21.8
Years Quit	10.0 ± 8.4
Years Follow Up	3.97 ± 2.11
Screening Group:	
NCCN Group 1	3657 (78.3%)
Emphysema (Yes)	2665 (57.0%)
Mild	1839 (39.4%)
Moderate	594 (12.7%)
Marked	178 (3.8%)
Not scored	54 (1.2%)
CAC (Yes)	3632 (77.7%)
Mild	1308 (28.0%)
Moderate	1128 (24.1%)
Marked	1195 (25.6%)
Not scored	0 (0%)

Table 2:

multivariable analyses for model all cause, COPD and pneumonia admissions.

Multivariable	All-cause hospital admission		COPD		Pneumonia	
	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value
CAC Extent	1.12 (1.06–1.18)	<0.001	1.19 (1.01–1.41)	0.036	1.26 (1.08–1.48)	0.004
None	Reference		Reference		Reference	
Mild	1.21 (1.02–1.44)	0.032	2.30 1.31–4.03)	0.004	1.48 (0.88–2.47)	0.140
Moderate	1.11 (0.92–1.34)	0.263	2.17 (1.20–3.91)	0.010	1.54 (0.90–2.64)	0.111
Marked	1.48 (1.23–1.78)	<0.001	2.27 (1.24–4.15)	0.008	2.19 (1.30–3.71)	0.003

adjusted for age, sex, race, BMI, current smoking status, pack years of smoking, emphysema severity and NCCN group.

Table 3:

Cox Multivariable analyses for all-cause mortality, CHF, AMI and Stroke admission.

Multivariable	All-cause mortality		CHF		AMI		Stroke	
	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value
CAC Extent	1.36 (1.20–1.55)	<0.001	1.27 (1.00–1.62)	0.049	1.49 (1.12–1.99)	0.007	1.56 (1.15–2.12)	0.005
None	Reference		Reference		Reference		Reference	
Mild	1.33 (0.84–2.10)	0.218	1.38 (0.61–3.13)	0.438	1.78 (0.55–5.85)	0.338	2.85 (0.79–10.33)	0.110
Moderate	1.49 (0.95–2.36)	0.084	1.46 (0.63–3.36)	0.377	4.81 (1.61–14.34)	0.005	3.62 (1.00–13.03)	0.049
Marked	2.48 (1.60–3.85)	<0.001	2.16 (0.96–4.86)	0.062	3.66 (1.17–11.52)	0.026	5.45 (1.53–19.39)	0.009

All-cause mortality adjusted for age, sex, race, BMI, current smoking status, pack years of smoking, emphysema severity and NCCN group. CHF, AMI and stroke adjusted for age, sex, race and pack years of smoking.

Table 4.

Active smoking, total cholesterol<200, LDL <130. HDL>40 and systolic BP <140 in patients with in network primary care physicians.

N = 3,226 (69%)	No CAC	Mild CAC	Moderate CAC	Marked CAC
Active smoking	370 (53.7%)	500 (54.4%)	418 (54.0%)	406 (48.2%)
Total Cholesterol <200	342 (55.4%)	476 (58.6%)	420 (60.3%)	578 (76.0%)
Systolic BP < 140	591 (86.4%)	730 (79.9)	615 (80.3%)	641 (76.5%)

Table 5.

LDL control in active smokers with moderate and marked CAC on baseline CTLS exam with in network primary care physicians.

Active smoking n 1,695 (52.5%)	Moderate CAC n 371 (21.9%)	Marked CAC n 359 (21.2%)
LDL <130	271 (73.1%)	305 (85.0%)
LDL <100	150 (40.4%)	214 (59.6%)