ORIGINAL ARTICLE

Automated Measurement of Coronary Artery Calcifications and Routine Perioperative Blood Tests Predict Survival in Resected Stage I Lung Cancer

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ABSTRACT

Introduction: Coronary artery calcification (CAC) is a well-known cardiovascular risk factor. In the past year, the CAC score has been investigated in lung cancer (LC) screening, suggesting promising results in terms of mortality risk assessment. Nevertheless, its role in patients with LC is still to be investigated. This study aimed to evaluate the performance of a fully automated CAC scoring alone and combined with a prognostic index on the basis of perioperative routine blood tests in predicting 5-year survival of patients with stage I LC.

Methods: This study included 536 consecutive patients with stage I LC who underwent preoperative chest computed tomography followed by surgical resection. The CAC score was measured by commercially available, fully automated artificial intelligence software. The primary outcome was the 5-year overall survival rate.

Results: A total of 110 patients (20.5%) had a CAC score greater than or equal to 400, 149 (27.8%) between 100 and 399, and 277 (51.7%) had less than 100. Male smokers had the highest CAC values: 32% compared with only 17% of nonsmokers. Females had lower CAC values compared with males both in smokers and nonsmokers: CAC greater than or equal to 400 only for 10% of smoking females and 0% in nonsmoking females. The 5-year survival was 80.3% overall, 84.7% in CAC less than 100, 77.5% in CAC 100 to 399, and 73.5% in CAC greater than or equal to 400 ($p = 0.0047$).

Conclusions: We observed that the CAC score predicted the 5-year overall survival in patients with resected stage I LC, both alone and combined with the modified routine blood test score. These results open new prospects for the prevention of noncancer mortality in patients with early-stage LC.

Keywords: Stage I lung cancer; Coronary artery calcification; Routine blood tests; Artificial intelligence

Introduction

Lung cancer (LC) remains one of the most common and most lethal malignancies globally. In Italy, in 2023, the number of new LC cases increased from 376,600

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(194,700 in men and 181,900 in women) to approximately 395,000 (208,000 in men and 187,000 in women).[1] The outcomes of LC patients, even in the earliest stages of the disease, though improved throughout the years, are still far from satisfactory.[2]

The introduction of effective screening methods, the development of advanced surgical techniques, and the breakthrough of innovative treatment strategies have been instrumental in improving patient outcomes.[2–4] The implementation of low-dose computed tomography (LDCT) imaging has facilitated the early detection of stage I LC. These imaging techniques not only allow for the measurement of disease extension but also provide clinically useful data on incidental findings, including coronary artery calcification (CAC).[5–7] CAC is an independent predictor of cardiovascular risk factors and it has turned out to be a reliable tool for noncancer-specific survival.[8,9] Recent studies in LC screening cohorts have found that fully automated artificial intelligence–based CAC scoring can predict all-cause mortality.[9–11]

Because all patients diagnosed with stage I LC have undergone at least a preoperative computed tomography (CT) scan, this could be useful for evaluating individual cardiovascular risk through CAC scoring. Incorporating this additional information could be critical in comprehensively understanding a patient's overall health, allowing for a tailored treatment plan for each patient.

Furthermore, accumulating evidence suggests that inflammatory and metabolic statuses have a considerable impact on patient outcomes,[12–14] and several indices for prognostication have been developed.[15] Internally, our study group has developed and validated a prognostic index on the basis of routine blood tests (RBTs). The RBT score aims to capture metabolic and inflammatory profiles, thereby predicting outcomes for patients undergoing pulmonary resection with curative intent.[16]

In this article, we aimed to assess the role of CACs in predicting outcomes for patients with stage I LC. In addition, we sought to combine data on CACs with the RBT score, potentially identifying a useful preoperative tool for predicting survival in early-stage LC.

Materials and Methods

Study Participants

This is a retrospective, observational, single-center cohort study. The study included 536 patients with pathologic stage I LC according to the eighth TNM classification[17] who were upfront surgically treated with radical intent between 2011 and 2022 at the Fondazione Istituto di Ricovero e Cura a Carattere Scientifico, Istituto Nazionale dei Tumori di Milano (Milan, Italy). All these patients underwent a preoperative CT scan with a 128-slice scanner. A written informed consent allowed the use of data for future research, including the present analyses.

Imaging Acquisition and Reconstruction

For this analysis, we considered for all patients the latest preoperative CT scan.

CT scans (either chest or chest-abdominal CT) were obtained with three different CT scanners (SOMATOM Flash, SOMATOM Force, SOMATOM Scope, Siemens Healthineers, Erlangen, Germany) and through different acquisition protocols. Chest CT images were reconstructed using a slice thickness of 1 to 5 mm.

Automated Measurement of CACs

CT images were transferred to a dedicated graphic station (Alienware Area 51 R6 equipped with Dual NVIDIA GeForce RTX 2080 OC graphics) and the CAC score was automated and quantified by commercial artificial intelligence software (AVIEW, Coreline Soft, Seoul, Korea) on the basis of a 3-dimensional U-net architecture[18]

CAC was assessed using the Agatston score and stratified into the following strata: less than 100, 100 to 399, and greater than or equal to 400.[19]

Modified RBT

RBT score, described elsewhere,[16] were composed of inflammatory, immunologic, and metabolic profiles on the basis of preoperative blood tests.

However, in this cohort, the glycemic index profile was missing for 60% (322 of 536) of patients. To address this, we developed a modified RBT score excluding the glycemic index while following the original formula. Consequently, we recalculated the cutoff points for the modified (modified RBT [m-RBT]) score on the basis of the percentiles obtained with this new formula. Patients were then categorized on the basis of the new percentiles: 0 to 8 (low-risk), 9 to 13 (intermediate risk), and greater than or equal to 14 (high-risk). The discriminatory power of the m-RBT was assessed using the ROC curves and the corresponding area under the curve (Supplementary Fig. 1).

Outcomes, Clinical, and Follow-Up Data

The primary end point was to assess the impact of the CAC score alone and combined with the preoperative m-RBT score on 5-year overall survival (OS), which was defined as the time from the date of the surgical procedure to the date of death from any cause or the last follow-up (June 2023). Vital status and date of death were obtained from the Istituto Nazionale di Statistica (ISTAT) using the SIATEL 2.0 (Agenzia Entrate, Rome, Italy) platform.

Patients were classified into three groups as follows: (1) low-risk: CAC less than 100 and m-RBT low or

intermediate; (2) moderate risk: CAC less than 100 and m-RBT high, CAC 100 to 399 and m-RBT low or intermediate or high, CAC greater than or equal to 400 and m-RBT low or intermediate; and (3) high risk: CAC greater than or equal to 400 and m-RBT high. Secondary end points were 90-day and 1-year postoperative mortality rates across the CAC and m-RBT score groups. Clinical and demographic data were collected from patients' medical records.

Statistical Analysis

Descriptive statistics were reported for categorical variables as counts and percentages, whereas for continuous variables, as medians with interquartile ranges (IQRs). Associations were assessed using the Cochran-Mantel-Haenszel test for trends with categorical data and the Jonckheere-Terpstra test for trends with continuous variables. Kaplan-Meier curves were estimated for a 5-year OS. Comparisons were tested by log-rank test for trend. Univariate Cox proportional hazard regression was used to estimate the 5-year OS hazard ratio (HR) with a 95% confidence interval (CI). Model 1 estimated the effect of CAC score alone; model 2, the effect of m-RBT score alone; and model 3, the effect of CAC and m-RBT combined.

The goodness of fit of each model is expressed as −2 log-likelihood (−2 logL): the lower the value gained, the higher the reliability of the model. A multivariate Cox model (model 4), adjusted for sex, age, smoking history, and stage of LC, was then built only for the model with the lowest -2logL values. The analyses were performed using the Statistical Analysis System Software (Release SAS:9.04; SAS Institute, Cary, NC).

Results

CAC Score Distribution

The study included 536 patients with stage I LC. Among these, 51.7% (277 of 536) had CAC less than 100, 27.8% (149 of 536) CAC 100 to 399, and 20.5% CAC greater than or equal to 400 (Table 1).

CAC scores were significantly higher in males compared with females ($p < 0.0001$) and in older patients ($p = 0.022$). Smoking status revealed significant differences, current or former smokers had higher levels of CAC compared with never-smokers ($p < 0.0001$). However, C-reactive protein, m-RBT score, hospital length of stay, and LC histologic diagnosis did not exhibit significant trends in CAC score. A statistically significant trend was observed in levels of forced expiratory volume in 1 second, stage of LC, and CAC score ($p = 0.0002$ and $p = 0.0363$, respectively).

Among males, smokers were more likely to have a high CAC score (32% with CAC $\geq$ 400) compared with nonsmokers (17% with CAC $\geq$ 400) (Fig. 1). In females, only 10% of smokers had CAC greater than or equal to 400, whereas none of the nonsmokers had CAC greater than or equal to 400 (Fig. 1).

Survival Analysis for CAC and m-RBT Scores

The median follow–up time for the entire cohort was 3.7 years (IQR: 2.2–6.7) and only for alive patients 3.9 years (IQR: 2.3–6.9). The 5-year OS rate for the entire study cohort was 80.3% (95% CI: 75.9–84.1). Stratified by CAC levels, the 5-year OS rates were 84.7% (95% CI: 78.5–89.3) for patients with CAC less than 100, 77.5% (95% CI: 68.9–84.2) for those with CAC 100 to 399, and 73.5% (95% CI: 62.2–81.9) for those with CAC greater than or equal to 400 (Fig. 2*A*). The 5-year OS was 86.3% in patients with m-RBT low, 83.5 with m-RBT intermediate, and 70.9% with m-RBT high (Fig. 2*B*). Combining CAC and m-RBT scores, the 5-year OS rates were 88.0% for low-risk patients, 77.3% for moderate risk, and 64.7% for high-risk (Fig. 2*C*).

In the Cox proportional hazards model 1, both patients with CAC greater than or equal to 400 and CAC 100 to 399 had a statistically significant higher risk of death compared with those with CAC less than 100 (HR = 2.37, 95% CI: 1.37–4.11 and HR = 1.78, 95% CI: 1.05–3.00, respectively) (Table 2). In model 2, patients with m-RBT high had a statistically significant higher risk of death compared with those with m-RBT low or m-RBT intermediate (HR = 2.24, 95% CI: 1.44–3.49). Model 3 illustrated that HRs for the CAC and m-RBT score combined were statistically significant for moderate risk (HR = 2.52, 95% CI: 1.42–4.71) and high risk (HR = 4.63, 95% CI: 2.17–9.90). Model 3 illustrated better goodness of fit compared with models 1 and 2, thus, we conducted a multivariate Cox model adjusted for age, sex, smoking status, and stage of LC. Notably, a significantly higher risk of death remains in patients classified as high-risk compared with low-risk (HR = 2.55, 95% CI: 1.13-5.73).

The 90-day and 1-year postoperative mortality were stratified by CAC score and m-RBT score. Significant differences were observed between 90-day postoperative mortality in CAC score ($p = 0.0041$), and 1-year postoperative mortality in m-RBT score ($p < 0.0001$) (Supplementary Table 1).

Supplementary Figure 2 illustrates a 5-year OS stratified for the stage of LC and histology. Patients with stage IA had a significantly higher survival compared with patients with stage I*B* ($p = 0.0008$).

Discussion

The present study investigated the prognostic role of preoperative CACs and m-RBT in stage I LC patients, reporting several noteworthy findings. First, sex, age,

Table 1. Characteristics of the Study Cohort According to the Automated AI-Based CAC Scores

Study Cohort	Total N = 536	CAC<100 n = 277	CAC 100-399 n = 149	CAC 400+ n = 110	Trend *p* Value
Age					
<55 y	44 (8.2)	30 (68.2)	8 (18.2)	6 (13.6)	0.022[a]
55-69 y	262 (48.9)	144 (55.9)	72 (27.5)	46 (17.6)	
≥70 y	230 (42.9)	103 (44.8)	69 (30.0)	58 (25.2)	
Median (IQR)	68.6 (62.4-74.1)	67.6 (60.5-72.8)	69.5 (63.6-74.0)	70.8 (65.9-76.0)	0.0002[b]
Sex					
Males	302 (56.3)	113 (37.4)	96 (31.8)	93 (30.8)	<0.0001[a]
Females	234 (43.7)	164 (70.1)	53 (22.6)	17 (7.3)	
Smoking Status					
Smokers	191 (35.6)	89 (46.6)	57 (29.8)	45 (23.6)	<0.0001[a]
Former smokers	249 (46.5)	117 (47.0)	72 (28.9)	60 (24.1)	
Nonsmokers	96 (17.9)	71 (74.0)	20 (20.8)	5 (5.2)	
CRP					
<2	237 (44.2)	136 (57.4)	57 (24.1)	44 (18.6)	0.1602[a]
2-4	177 (33.0)	82 (46.3)	58 (32.8)	37 (20.9)	
≥5	122 (22.8)	59 (48.4)	34 (27.9)	29 (23.8)	
RBT					
Low	180 (33.6)	99 (55.0)	52 (28.9)	29 (16.1)	0.3325[a]
Intermediate	192 (35.8)	101 (52.6)	48 (25.0)	43 (22.4)	
Higher	164 (30.6)	77 (47.0)	49 (29.9)	38 (23.2)	
FEV1 %					
Median (IQR)	96 (80-109)	100 (84-112)	93 (77-109)	89.5 (73-123)	0.0003[b]
Hospital length of stay					
Median (IQR)	5 (4-7)	5 (4-7)	5 (4-7)	5 (4-8)	0.5608[b]
Stage					
IA	325 (60.6)	177 (54.5)	93 (28.6)	55 (16.9)	0.0363[a]
IB	211 (39.4)	100 (47.4)	56 (26.5)	55 (26.1)	
Histology					
Adenocarcinoma	390 (72.8)	204 (52.3)	100 (25.6)	86 (22.1)	0.1268[a]
Other[c]	146 (27.2)	73 (49.7)	49 (33.3)	24 (16.4)	

[a]Cochran-Mantel-Haenszel test.
[b]Jonckheere-Terpstra test.
[c]Other: Carcinoma not otherwise classified (n = 4), Squamous cell carcinoma (n = 83), Large cell carcinoma (n = 6), Small cell carcinoma (n = 3), Undifferentiated carcinoid (n = 2), Typical carcinoid (n = 27), Atypical carcinoid (n = 5), Neuroendocrine carcinoma (n = 12), sarcoma (n = 1), Other tumor not otherwise classified (n = 3).
CAC, coronary artery calcification; IQR, interquartile range; CRP, C-reactive protein; RBT, routine blood test; FEV1%, forced expiratory volume in 1 second.

and smoking status influence the values of CAC detected during the preoperative CT scan. Second, the presence and severity of CACs influence the outcomes of stage I LC. Third, incorporating the evaluation of CACs into the m-RBT provides a better score for accurately predicting survival in patients with stage I LC.

The growing adoption of screening methods for the early detection of LC allows a higher detection of incidental findings beyond LC itself. One of the most common incidental findings observed during LDCT is subclinical coronary arteriosclerosis (i.e., CAC). The prevalence of CAC among the screened population is generally higher than 10%. In fact, CAC and LC share some risk factors, including older age and (heavy) smoker status.[20] The American College of Radiology recommended reporting CACs detected during LDCT, even in patients without symptoms.[21] Including the calcifications detection in LC screening will refine the selection of those who are most at risk and who could benefit most from preventive interventions such as smoking cessation or anti-inflammatory therapy. Indeed, CAC represents one of the main risk factors for coronary arteriosclerotic disease (CAD) and other pathologic conditions including dementia and other cardiovascular events.[22] Hence, the detection of CAC might represent a unique opportunity to implement a therapeutic preventive strategy to reduce the burden of CAD.[21,22] Joshi et al.,[23] in the Multiethnic Study of Atherosclerosis, evaluated long-term outcomes of individuals at risk for cardiovascular events. This study, involving more than 6800 participants without cardiovascular issues, suggested that CAC represents the strongest predictor of incident CAD.[23] Notably, CAC was present in 76% of participants who experienced an event. More recently, Mitchell et al.[24] evaluated more than 23,000 patients with a low burden of traditional

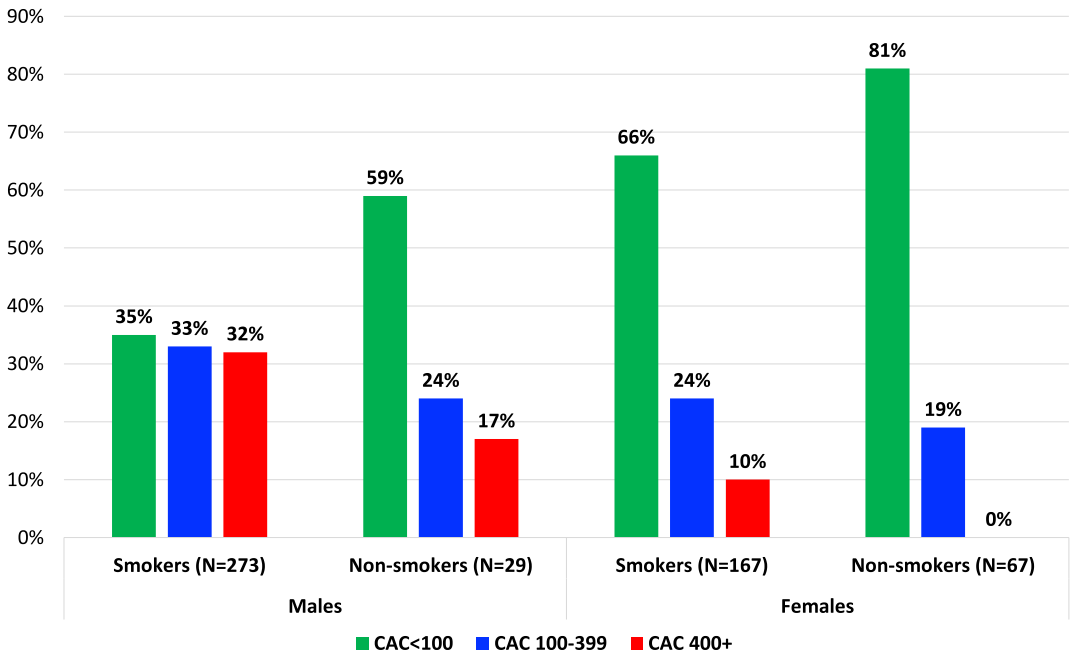

Figure 1. Distribution of the automated AI-based CAC score stratified by sex and smoking status. AI, artificial intelligence; CAC, coronary artery calcification.

risk factors for cardiovascular disease. Patients were evaluated over a median follow-up period of 11.4 years.

They suggested the importance of CAC, reporting that CAC less than 100, from 101 to 400, and greater than 400 correlated with a 2.2, 3.8, and 5.9 risk of having a myocardial infarction, respectively. Similarly, they observed that the risk of death was 1.2, 1.5, and 2.1 in individuals with a CAC less than 100, 101 to 400, and greater than 400, respectively ($p < 0.001$). Interestingly, we confirmed that, even in the LC population, detection of CAC is of paramount importance, being that CAC greater than or equal to 400 is associated with a nonnegligible increased risk of death compared with lower values.

In the era of precision medicine, there is a high demand to create accessible tools for predicting individual patient outcomes. Although advantages in molecular and genomic profiling offer robust data for prognosis and for optimizing targeted therapies, the incorporation of genetic tests into clinical practice is challenging. Costs, turnaround time, and the lack of solid evidence in localized diseases are the main barriers. Hence, the identification of easily available and reproducible tools is of paramount importance.[16] The RBT score brings this unmet need. Evaluating blood cell parameters, the RBT score allows the cluster of patients on the basis of inflammatory and metabolic characteristics, thus, being a useful tool in patients' prognostication.[16]

In the previous publication of our study group, we reported that inflammatory markers represent a useful tool for prognostication in patients with LC but also in patients affected by other solid tumors.[13] In the more recent research on this topic, 2088 and 1129 patients with LC and lung metastases were evaluated.[16] Patients with high RBT ($\geq$18) experienced a higher risk of 30-day and 5-year mortality in comparison to patients with low RBT.[16] Even in this cohort, the m-RBT score (assessing the inflammatory, immunologic, and metabolic profiles excluding the glycemic index) predicts 1-year LC survival. But more interestingly, we noted that combining CAC and m-RBT scores resulted in a more accurate tool for predicting patients' outcomes.

The main weaknesses of this study included the inherent biases of the retrospective nature of this study. A few other limitations need to be addressed. First, we just focused on stage I LC, and further studies in a broader LC population are needed. Second, we corrected our data for many measurable variables; however, there are many potential measurable and nonmeasurable variables influencing the interpretation of our result. Third, CT scans were acquired with different scanners and protocols. Finally, external validation of our study is needed.

Conversely, the main strengths of the present investigation include its innovative nature and its potential clinical application: inexpensive and nonharmful data derived from routinary diagnostic exams, either radiologic or biochemical, could contribute to establishing an easy-to-use prognostic tool, capable of determining nutritional, metabolic, and immunologic status of a patient and to predict his long-term survival rates. In

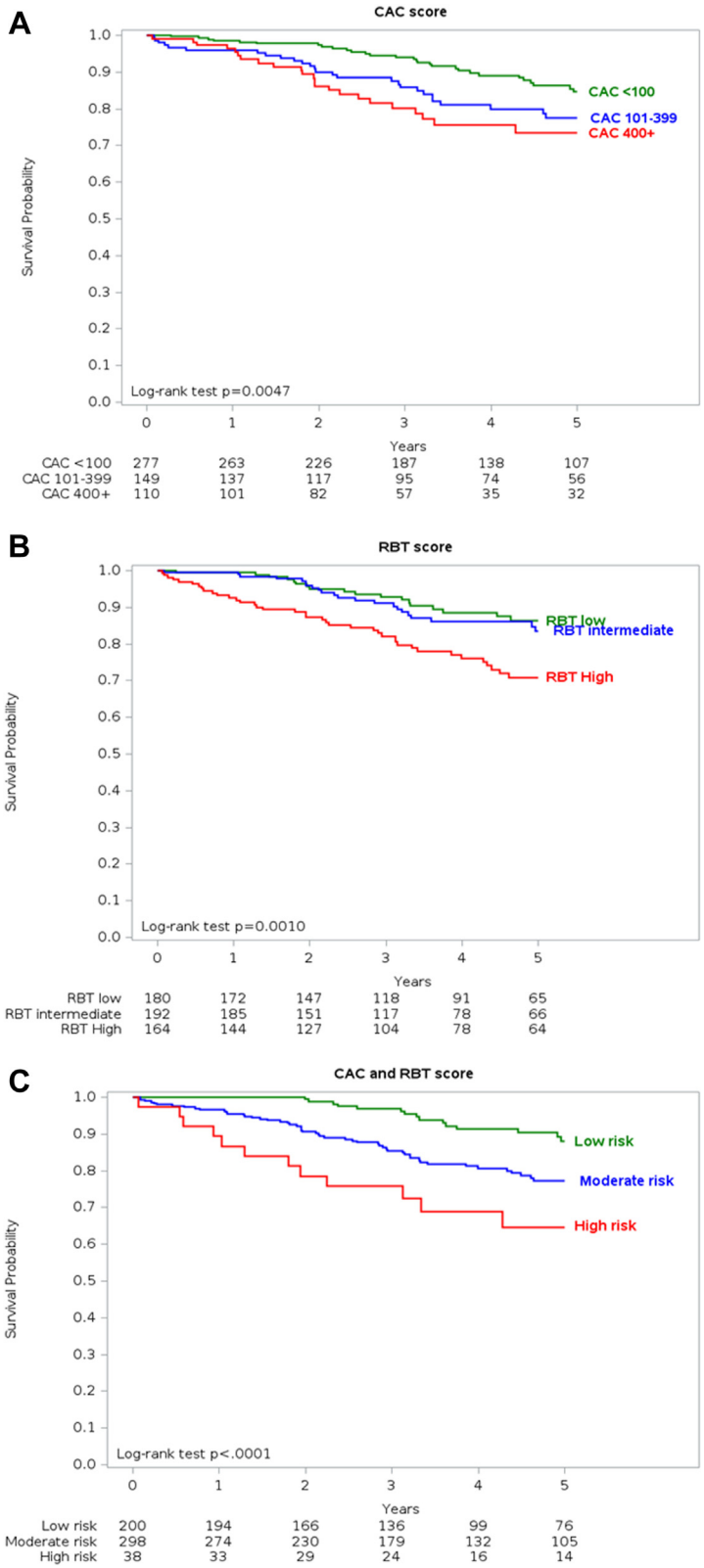

Figure 2. 5-year OS for the automated AI-based CAC score (*A*); RBT score (*B*); and CAC and RBT scores combined (*C*). AI, artificial intelligence; CAC, coronary artery calcification; OS, overall survival; RBT, routine blood test.

Table 2. Cox Proportional Hazards Regression Models Stratified by Automated AI-Based CAC Score, RBT Score, and RBT Plus CAC Score Combination

Mortality Models		Total	5-year mortality	Model 1	Model 2	Model 3	Model 4[a]
		N = 536	n = 79 (14.7)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)
CAC	<100	277	29 (10.5)	1			
	100-399	149	27 (18.2)	1.78 (1.05-3.00)			
	400+	110	23 (20.9)	2.37 (1.37-4.11)			
RBT	low+int	372	40 (10.8)		1		
	high	164	39 (23.8)		2.24 (1.44-3.49)		
RBT+CAC	RBT- CAC<100	300	15 (7.5)			1	1
	Other	298	52 (17.4)			**2.52 (1.42-4.71)**	1.73 (0.95-3.17)
	RBT+ and CAC 400+	38	12 (31.6)			**4.63 (2.17-9.90)**	2.55 (1.13-5.73)
−2 LOG L				926.98	924.79	**919.13**	897.34
AIC				930.98	926.79	**923.13**	913.34

Note: Boldface for statistically significant estimates.
[a]Adjusted for age, sex, smoking status, and stage of LC.
−2 LOG L, -2 times the log likelihood; AI, artificial intelligence; AIC, Akaike's information criteria; CAC, coronary artery calcification; CI, confidence interval; HR, hazard ratio; int, intermediate; LC, lung cancer; RBT, routine blood test.

addition, the article includes a relatively large sample size of patients with LC undergoing CT.

In conclusion, the present article suggested the importance of searching for CAC and testing for m-RBT scores at the diagnosis of early-stage LC. Indeed, the presence of significant CAC and unfavorable m-RBT score correlates with an increased risk of death, which might be lowered by counseling and targeted interventions. Indeed, by merging those data, we are able to achieve a more holistic evaluation of patients' metabolic and immunologic status, thus, gaining a useful tool for patients' prognostication. Potentially in future research, the identification of patients at risk might have also important preventive implications, for implementing compartmental, dietary and lifestyle, smoking cessation, and pharmacologic (e.g., low-dose aspirin, statin, or antiplatelet therapy) interventions to reduce the risk of developing CAD over the medium- (>1 y) and long-term (>5 y) period. Moreover, targeting inflammation and improving metabolic status might be useful in improving the outcomes of patients with cancer. Growing evidence supports that reducing inflammation and improving nutrition resulted in a reduced risk of death in patients with cancer.[25,26]

This study highlights that the unrecognition of CAC in CT could mean missing a valuable opportunity to identify subclinical cardiovascular disease in patients with LC and to guide preventive cardiologic intervention to reduce the burden of CAD. Equally, disregarding the baseline nutritional and immunologic status of the patient, as derived by m-RBT, could potentially prevent us from properly correcting disadvantageous conditions. Further prospective experience and interventional studies are warranted.

CRediT Authorship Contribution Statement

Federica Sabia: Data curation, Methodology, Formal analysis, Data interpretation, Writing - original draft, Writing - review & editing.

Camilla Valsecchi: Data curation, Methodology, Formal analysis, Data interpretation, Writing - original draft, Writing - review & editing.

Roberta Eufrasia Ledda: Data curation, Writing - original draft, Writing - review & editing.

Giorgio Bogani: Writing - original draft, Writing - review & editing.

Riccardo Orlandi: Writing - original draft, Writing - review & editing.

Luigi Rolli: Writing - review & editing.

Michele Ferrari: Writing - review & editing.

Maurizio Balbi: Data curation, Writing - original draft, Writing - review & editing.

Alfonso Marchianò: Writing - review & editing.

Ugo Pastorino: Conceptualization, Data curation, Methodology, Formal analysis, Data interpretation, Writing - original draft, Writing - review & editing.

Data Availability

The study data are available on reasonable request to the corresponding author (Dr. Pastorino).

Disclosure

The authors declare no conflict of interest.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2025.100788

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