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Research article

Pulmonary Circulatory System: A Biomarker for Lung Cancer Development

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Abstract

This study aimed to investigate the relationship between the morphology of pulmonary circulatory system and lung cancer development based on low dose computed tomography (LDCT) scans acquired in the screening setting. We analyzed the baseline LDCT scans in the Pittsburgh Lung Screening Study (PLuSS) cohort, including 3,635 patients who underwent screening between 2002 and 2016. The analysis showed that pulmonary circulatory system characteristics, particularly intrapulmonary vein volume, are important predictors of lung cancer development. The joint model of circulatory structures revealed a strong prognostic ability of the intrapulmonary vessel ratio, achieving an AUC of 0.69 (95% CI: 0.66-0.72). Adjusting for non-circulatory parameters, intrapulmonary vessel ratio remained strongly prognostic ($p<0.001$), with cross-validated combined scores showing substantial improvement in prognostic ability (HR=2.20, 95%CI: 2.00-2.43; AUC=0.74, 95%CI: 0.71-0.77). The overall composite model, incorporating heart volume and BMI, achieved slightly better prognostic ability with an AUC of 0.76 (95%CI: 0.73-0.78). The addition of circulatory structures allowed identifying approximately 10% of the population with risk several times greater than average, with a 30% risk (95% CI: 0.26-0.35 for cumulative incidence) of developing lung cancer within 15 years. These findings suggest that incorporating pulmonary circulatory system characteristics in LDCT screening programs can improve their efficiency in identifying individuals at risk of developing lung cancer, particularly in the long term.

Key words: lung cancer, image biomarker, low dose computed tomography, risk factor, pulmonary vasculature

Introduction

Lung cancer is responsible for a staggering 25% of all cancer-related deaths in the United States (U.S.) [1, 2]. The high mortality is partly attributed to the lack of early-stage symptoms and limited access to screening. The National Lung Screening Trial (NLST) showed that low-dose computed tomography (LDCT) scans can reduce lung cancer-related deaths by approximately 20% in comparison to chest X-rays [3, 4]. As a result, the Center for Medicare and Medicaid Services (CMS) has decided to cover annual lung cancer screening with LDCT scans for asymptomatic adults with a history of tobacco smoking. The NLST findings served as the primary motivation for this decision. In 2021, the U.S. Preventive Services Task Force (USPSTF) updated its recommendation for annual lung screening with LDCT.

The updated guideline recommends annual screening for adults aged 50 – 80 years with a tobacco smoking history of 20 pack-years or more who either smoked or quit within the past 15 years [5]. The updated recommendation expands the population eligible for LDCT lung screening by approximately 87%, resulting in 14.5 million people in the U.S. being eligible for screening [6]. This eligibility expansion results in a 107% increase in Black adults, a 112% increase in Hispanic adults, and a 96% increase in women [6]. Tobacco smoking remains the primary risk factor determining an individual's eligibility for LDCT lung screening.

Despite the promise of LDCT for lung cancer screening, the results from NLST show that only a small percentage of patients who underwent the procedure were diagnosed with lung cancer[3, 4]. Out of the 53,454 smokers enrolled in the study, only 3.85% (2,058 subjects) were diagnosed with lung cancer, indicating that the majority of screened subjects did not develop the disease but are still recommended to have annual LDCT scans. This will not only cause unnecessary radiation exposure to those healthy subjects but also impose significant economic burden on public health and low-income families. Additionally, it is worth mentioning that there are still 16% of women and 10% of men who never smoke but are diagnosed with lung cancer [7, 8], underscoring the need for identifying additional biomarkers that can accurately assess the risk of developing the disease. The high cost and exposure to unnecessary radiation associated with LDCT scans also highlight the importance of finding more reliable methods for predicting lung cancer risk, by which a large portion (e.g., 30%–50%) of subjects eligible for LDCT lung cancer screening can be excluded from unnecessary annual screening (e.g., subjects with low risk of lung cancer will have an LDCT scan every 2–3 years instead of every year). Additionally, the reduction of unnecessary screening by this personalized strategy could potentially further expand the eligibility for lung cancer screening without incurring additional cost burden.

In this study, we leveraged an ongoing lung cancer screening program, namely the Pittsburgh Lung Screening Study (PLuSS) 9 starting in 2002, to systematically study the underlying relationship between pulmonary circulatory system (PCS) and lung cancer development. The goal is to clarify whether the morphological characteristics of PCS can serve as risk predictors for lung cancer. The underlying rationale of this study is that lung cancer development cannot be independent of its surrounding structures, especially the PCS that is responsible for deliver oxygen and nutrition to the lungs.

Methods

Study population

We used a community-based research cohort, the Pittsburgh Lung Screening Study (PLuSS) (IRB # 21020128), to test the premise and develop the prediction models. The PLuSS cohort enrolled 3,642 current and ex-smokers, screened with baseline LDCT between 2002 and 2005, and followed for lung cancer 9. Excluded were individuals who: 1) quit smoking >10 years earlier, 2) reported a history of lung cancer, or 3) reported chest CT within one year of enrollment. Demographic and smoking history data were collected using structured interviews and questionnaires at baseline, and smoking status is updated yearly. Upon study entry, participants underwent LDCT screening. Seven patients enrolled in PLuSS but later refused the CT scan. As a result, this cohort has 3,635 patients observed from 2002 to 2016 (Supplementary Table 1), which were involved in the data analyses. There were 1,866 men and 1,769 women, 94.2% white, 5.2% black, and 0.6% other non-white race. Mean age at enrollment was 59.58 years, 60.2% were current smokers, 10% had a history of COPD, and 20.6% had a family history of lung cancer involving a parent or sibling. The cohort approximately equally represents males and females of predominantly white, older than 44, and include more than 60% of the current smokers.

As of the analysis cutoff date (07/30/2021), 1,218 (29.0%) patients have died and 385 (10.6%) have developed lung cancer (including 282 patients who have died thereafter). Hence, 936 patients have died without known cancer. Among 1,218 patients who had died, approximately 138 (11.3%) died within 4 years, 370 (30.4%) within 8 years, and 690 (56.7%) within 12 years. Among 385 patients who had developed lung cancer, approximately 100 (25%) developed cancer within the first 4 years, and approximately 100 (25%) developed cancer after 12 years. The follow-up time ranged from 0.3 to 19 years with a median of 17.5 years (Kaplan-Meier estimate).

Pulmonary circulatory system (PCS) parameters

We used our available computer algorithms 10, 11 to automatically segment PCS structures, including pulmonary arteries and veins, as well as heart regions, on LDCT scans (Supplementary Figure 1). Utilizing the lung volume segmentation 12, we further differentiated intra- and extra-pulmonary arteries and veins. The volumes of these structures were calculated based on the segmentation results.

Statistical analysis

The analysis of time from the first CT to the lung cancer diagnosis, accounting for the competing event of death (PROC PHREG, SAS v.9.4, SAS Institute, Cary, NC) [13], was used to evaluate patient demographics and other baseline characteristics, as well as CT-derived PCS characteristics in predicting lung cancer in the future. Continuous parameters were normalized and standardized (to mean zero and variance of '1', after the logarithmic transformation) to improve the assessment's robustness, enable the evaluation of ratios of the parameters, and facilitate the comparison of the relative effects. Hazard ratio (HR) was used to assess individual significance univariately and in the combined models (using a forward selection approach verified by backward elimination). Five-fold cross-validation was used to evaluate multivariable models in terms of the prognostic score's (linear predictor's) HR for one standard deviation change, The standard time-dependent receiver operating characteristic (ROC) analysis was used to illustrate the prognostic ability of different models over the considered time range (by counting death before lung cancer being at risk at all considered time points). Based on observed lung cancer in approximately 10% of participants, the cross-validated prognostic score of the overall model was used to define the risk strata by grouping the top 10% of participants as "high risk", the bottom 50% as "low risk", and the remaining as "intermediate risk". Cumulative incidence function and Gray's test (PROC LifeTest, SAS v.9.4) were used to evaluate the final risk strata.

Results

Cumulative incidence function and overall survival

Supplementary Table 2 summarized the computed PCS parameters based on the LDCT scans in our cohort. Based on our study cohort with a cutoff day of 07/30/2021, the cumulative incidence rate of lung cancer reached 11.2% and the overall survival rate dropped to 60% by 19 years. At 17.5 years, the incidence of lung cancer was 10.7%, and the overall survival rate was 67%, respectively. Participants in this cohort had an 80% chance to survive within 12 years from the first CT scan (approximately at the time of enrollment) with a 7.7% risk of developing lung cancer (Supplementary Figure 2).

Demographics and future lung cancer development

Supplementary Table 3 summarizes the hazard ratios of lung cancer and the corresponding p-value for the demographic and other characteristics of the study participants. Among the patient characteristics, the presence of emphysema had the strongest association with future lung cancer (HR= 2.5, p<0.0001). In the multivariant model, only age, smoking, and emphysema remained statistically significant predictors. Adjustment for these factors reveals no meaningful association between BMI and future lung cancer in this cohort (HR=0.99, p=0.86). The standalone relevance of BMI appeared to be confounded by the smoking and emphysema statuses, as current smoking and/or emphysema were associated with lower BMI.

The cross-validated prognostic score based on age, smoking status, and emphysema showed moderate predictivity for future lung cancer (HR=1.87, 95% CI: 1.69-2.07, per a change of one standard deviation). However, its prognostic ability gradually diminishes over a longer time span, with the cross-validated time-dependent AUC decreasing from 0.74 (95%CI: 0.70-0.77) at 5.5 years to 0.69 (95% CI: 0.66-0.72) at 15 years after the baseline CT scan (Supplementary Figure 3). Therefore, there is a greater potential, and the need, for improving the long-term prognostic ability.

CT-derived PCS parameters and future lung cancer development

Supplementary Table 4 presents the hazard ratios and the corresponding p-values for five circulatory parameters considered in predicting future lung cancer (significant associations were determined based on the Bonferroni adjustment with p<0.01). Among the circulatory parameters, intrapulmonary vein volume was univariately the strongest predictor of future lung cancer (HR=0.63, p<.001, per one standard deviation change of a log-transformed volume). This parameter maintained a consistently strong effect in a joint model. The other parameters, including some of the univariately significant ones (extrapulmonary vein volume, HR=0.84, p=0.001), played supportive roles with variable effects in the joint model. For example, extrapulmonary vein volume (HR=0.97, p=0.63) was replaced by extrapulmonary artery volume (HR=1.59, p<0.001).

The joint model coefficients for log-transformed intrapulmonary artery and vein volumes were 0.46 and -0.90, respectively (as logs of hazard ratios, Supplementary Table 4), suggesting the relevance of the ratio of the intrapulmonary artery volume to the square of the intrapulmonary vein volume as a predictor of future lung cancer. This intrapulmonary vessel ratio provides greater interpretability of circulatory structures and shows a strong standalone association with future lung cancer (HR=1.78, 95% CI: 1.61-1.94, per one-standard-deviation change), resulting in a 15-year AUC of 0.69 (95% CI: 0.66-0.72). The addition of extrapulmonary artery volume significantly improves the joint model (HR=1.2, p<0.001) and sharpens the effect of the intrapulmonary vessel ratio (HR=1.85, p<0.001), but does not meaningfully improve the long-term prognostication of lung cancer. The cross-validated prognostic score had a 15-year AUC of 0.70 (95% CI: 0.67-0.73) (Supplementary Figure 4).

Composite model for predicting future lung cancer

The intrapulmonary vessel ratio remains strongly a strong prognostic factor even after the adjustment for non-circulatory parameters, including age, smoking status, and emphysema, with an HR=1.85 (95% CI: 1.66-2.07). The cross-validated combined score showed a meaningful improvement over the circulatory or demographic models with an HR=2.20 (95% CI:2.00-2.43) and a 15-year AUC of 0.74 (95% CI: 0.71-0.77).

The overall composite model, which incorporates circulatory parameters, demographic and other baseline characteristics of participants, can be further improved by incorporating heart volume and BMI (HRs per one-standard-deviation change of 1.14, p<0.001, and 0.88, p=0.0146). We note that based on the model's estimated coefficients for the log-transformed heart volume and BMI (0.24 and -0.13 respectively), their joint effect can be effectively represented by a ratio of the heart volume to the squared root of BMI, which allows for better standalone interpretability.

The cross-validated prognostic score of the composite model provides distinct advantages over the models based solely on circulatory characteristics or only demographic and other baseline characteristics (Supplementary Figure 5). At 15 years, the cross-validated composite prognostic score shows a uniformly higher ROC curve with an AUC of 0.76 (95%CI: 0.73-0.78) and regular shape, indicating a similar ability to identify high and low-risk participants in the long term.

Risk stratification based on the composite model

To illustrate the prognostic ability of the composite model, we stratified participants into three risk strata based on the top 10% of the cross-validated overall prognostic score ("high risk"), the bottom 50% of the prognostic score (low risk), and the remaining participants ("intermediate risk"). Supplementary Table 5 summarizes the strata and their corresponding 15-year estimates of cumulative incidence function (CIF), while Supplementary Figure 6 shows the CIF curves. Compared to the low-risk stratum, the intermediate-risk stratum has an HR=3.2 (95% CI: 2.41-4.11), and the high-risk stratum has an HR=9.2 (95% CI: 6.91-12.19).

Discussion

We conducted a study using a large lung cancer screening cohort (n=3635) to investigate the relationship between pulmonary circulatory structures (PCS) and future lung cancer risk, while also taking into account non-circulatory parameters such as age, smoking status, emphysema, heart volume, and BMI. Our findings suggest that the intrapulmonary vessel ratio, defined as the ratio of intrapulmonary artery volume to the square of intrapulmonary vein volume, is a strong predictor of future lung cancer risk,

providing a more interpretable measure of circulatory structures. Incorporating non-circulatory parameters improves the accuracy of lung cancer prediction models and outperforms models based solely on circulatory or demographic parameters. Our composite model can identify patients with negligibly low risk of lung cancer as well as approximately 10% of the population with a risk several times greater than average. To our knowledge, our study is the first to demonstrate the prognostic ability of PCM in predicting lung cancer development. Furthermore, the computer algorithms used in this study to quantify relevant PCM features are fully automated for LDCT scans, making it relatively easy to implement this tool in a screening setting. Our study employs cross-validation to evaluate the accuracy and generalizability of the models, providing a robust assessment of their predictive ability.

One of the unique aspects of this study is the exploration of pulmonary circulatory characteristics as predictors of lung cancer risk. Awareness of these factors will help identify those who are at risk of developing lung cancer, refine the eligibility for LDCT lung cancer screening, and develop novel ways (e.g., breathing exercises) to change the PCM morphology, or potential chemoprevention strategies, and thus reduce the chance of developing lung cancer. As far as we are aware, no prior study has explored the underlying relationship between pulmonary circulatory structures, particularly the differentiation of lung arteries and veins, and the risk of developing lung cancer in the future. This is likely due to the difficulty in automatically identifying intra- and extrapulmonary arteries and veins on non-contrast CT scans. Given the prevalence of lung cancer and the wide adoption of LDCT lung cancer screening in the U.S. and worldwide, there could be significant potential clinical and translational implications. Our study also leverages one of the unique features of LDCT lung cancer screening, in that the LDCT provides detailed information about all anatomic structures in the thorax, beyond the presence or absence of suspicious findings for lung cancer. This is why LDCT, in contrast to all other cancer screening modalities, uniquely reduces all cause mortality, as well as lung cancer mortality[3]. Our results are one of the first studies to use data from the LDCT, present in all subjects screened (not just those with lung nodules) to predict lung cancer development.

Currently, the exact mechanism linking pulmonary circulatory parameters and future lung cancer risk is not fully understood. One possible explanation for the association between intrapulmonary vein volume and lung cancer risk is that alterations in the pulmonary vasculature may affect the oxygenation and nutrient supply to lung tissue, leading to cellular stress and potential tumor development. Intrapulmonary veins are responsible for draining deoxygenated blood from the lung tissue and returning it to the heart, and their volume may reflect the efficiency of this process. Alterations in intrapulmonary vein volume, such as dilation or constriction, could potentially affect blood flow and nutrient delivery to lung tissue, leading to cellular stress and creating an environment conducive to the development of cancerous cells. Moreover, changes in intrapulmonary vein volume may reflect alterations in the microenvironment of lung tissue, such as inflammation or fibrosis, which could also contribute to cancer development.

Interestingly, even after adjusting for non-circulatory parameters such as age, smoking status, and emphysema, the intrapulmonary vessel ratio remains a strong prognostic factor for future lung cancer risk. This suggests that the intrapulmonary vessel ratio captures a unique aspect of lung physiology that is distinct from these other risk factors. It is likely influenced by a variety of factors, such as smoking history, inflammation, and underlying lung diseases, which can affect the structure and function of blood vessels in the lung. Changes in the intrapulmonary vessel ratio may indicate alterations in the lung tissue's microenvironment, such as increased angiogenesis or vascular remodeling, known to be involved in the development and progression of lung cancer. Therefore, a higher intrapulmonary vessel ratio may indicate an increased risk of future lung cancer, while a lower ratio may suggest a healthier lung microenvironment and a lower risk of lung cancer.

Our study found that incorporating heart volume and BMI into the composite model improved the prediction of future lung cancer risk. To our knowledge, no study reported the underlying association between heart volume and lung cancer risk, while there are studies about the association between BMI and lung cancer risk [14-21]. The inverse association between BMI and lung cancer risk (Supplementary Table 3) as we found as consistent with many available studies [14-19]. However, it is unclear about the inverse association between heart volume and lung cancer risk.

Despite the promising findings, this study has some limitations. First, the study cohort was generated from a single medical institution. The enrolled patients were primarily distributed geographically across Western Pennsylvania, and majority of them were white. Second, our algorithms for segmenting various structures and tissues on LDCT scans are not perfect, our promising results on thousands of LDCT scans demonstrated their unique potential as novel biomarkers for predicting the risk of lung cancer. Also, we only measured the volume of the pulmonary circulatory structures and did not analyze other parameters such as diameters of the pulmonary circulatory structures, which may provide additional insights into their clinical potential for predicting lung cancer development. Finally, our analysis did not take into account the presence of suspicious nodules in this study, because a large portion of the enrolled subjects do not have suspicious lung nodule findings. Actually, we think this could also be considered a strength of this study, , in that it demonstrates the potential of these biomarkers in predicting lung cancer risk in patients without suspicious nodules.

Conclusion

Our study provided evidence that pulmonary circulatory parameters, especially the intrapulmonary vessel ratio, could serve as important predictors of future lung cancer risk. Their combination with subject demographics can allow outlining a sizable stratum of patients with negligibly low risk of lung cancer as well as identifying approximately a large portion of the population with risk several times greater than average, thereby improving the eligibility and enabling personalized LDCT lung screening. Nonetheless, further research is needed to better understand the underlying mechanisms and to validate these findings in larger and more diverse populations, as well as determine

whether additional imaging analysis of other thoracic structures (e.g., airways features) present on LDCT could be added to the pulmonary circulatory model.

Abbreviations

CT: computed tomography; LDCT: low-dose computed tomography; ROC: receiver operating characteristics; AUC: area under the curve; NLST: the national lung screening trial; CMS: center for medicare and medicaid services; PLuSS: Pittsburgh lung screening study; PCS: pulmonary circulatory system; CI: confidence interval; HR: hazards ratio;

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Conflicts of Interest

The authors have no conflict of interest to declare.

Informed Consent

Written informed consent was waived by the Institutional Review Board.

Ethical Approval

This study was approved by the University of Pittsburgh Institutional Review Board (IRB) (IRB #: 21020128).

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