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Relationship between Incidental Abnormalities on Screening Thoracic Computed Tomography and Mortality: A Long-Term Follow-Up Analysis

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Objective: The present study aimed to assess the relationship between incidental abnormalities on thoracic computed tomography (CT) and mortality in a general screening population using a long-term follow-up analysis.

Materials and Methods: We retrospectively collected the medical records and CT images of 840 participants (mean age ± standard deviation [SD], 58.5 ± 6.7 years; 564 male) who underwent thoracic CT at a single health promotion center between 2007 and 2010. Two thoracic radiologists independently reviewed all CT images and evaluated any incidental abnormalities (interstitial lung abnormality [ILA], emphysema, coronary artery calcification [CAC], aortic valve [AV] calcification, and pulmonary nodules). Kaplan–Meier analysis with log-rank and z-tests was performed to assess the relationship between incidental CT abnormalities and all-cause mortality in the subsequent follow-up. Cox proportional hazards regression was performed to further identify risk factors of all-cause mortality among the incidental CT abnormalities and clinical factors.

Results: Among the 840 participants, 55 (6%), 171 (20%), 288 (34%), 396 (47%), and 97 (11%) had findings of ILA, emphysema, CAC, pulmonary nodule, and AV calcification, respectively, on initial CT. The participants were followed up for a mean period ± SD of 10.9 ± 1.4 years. All incidental CT abnormalities were associated with all-cause mortality in univariable analysis ($p < 0.05$). However, multivariable analysis further revealed fibrotic ILA as an independent risk factor for all-cause mortality (hazard ratio, 2.52 [95% confidence interval, 1.02–6.22], $p = 0.046$). ILA were also identified as an independent risk factor for lung cancer or respiratory disease-related deaths.

Conclusion: Incidental abnormalities on screening thoracic CT were associated with increased mortality during the long-term follow-up. Among incidental CT abnormalities, fibrotic ILA were independently associated with increased mortality. Appropriate management and surveillance may be required for patients with fibrotic ILA on thoracic CT obtained for general screening purposes.

Keywords: *Screening population; Interstitial lung abnormality; Mortality; Long-term follow-up analysis*

INTRODUCTION

Aging and death are inevitable, natural processes

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triggered by biological and environmental factors. Aging of the lung contributes to a gradual decline in lung function, and is a major risk factor for lung diseases such as idiopathic pulmonary fibrosis (IPF) and chronic obstructive pulmonary disease (COPD) [1,2]. Aging is also associated with vascular calcification, such as coronary artery calcification (CAC) and aortic valve (AV) calcification, which are both major risk factors for heart disease [3]. Lung and heart diseases have risen to become the leading causes of death in the United States in the last 5 years [4]. Computed tomography (CT) has been used as a diagnostic tool for such conditions for decades. Incidental abnormalities on CT

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have drawn attention in recent years as representative of a subclinical stage of disease, or as prognostic signatures of aging and death. Managing incidental findings on thoracic CT is important, as its incidence gradually increases with the increase in the aging population and the rapid rise in the popularity of CT for screening purposes, such as lung cancer screening [5].

Interstitial lung abnormalities (ILA), emphysema, and CAC are the representative incidental abnormalities detected on thoracic CT and are associated with increased mortality [6-8]. CAC is reported in approximately 50% of patients undergoing CT examinations for non-cardiac indications [9]. Pulmonary nodules are also commonly encountered on thoracic CT, accounting for approximately 30% of chest CTs [10]. A recent study demonstrated mortality reduction with lung cancer screening; therefore, appropriate management of pulmonary nodules is strongly recommended among high-risk populations [11]. AV calcification is not frequently encountered in the general screening population compared with the aforementioned abnormalities; however, it is associated with the occurrence of adverse events, such as valve replacement and mortality [12].

These abnormalities share similar pathomechanisms, such as older age, male sex, and smoking, and are associated with increased mortality; however, their effects on mortality may vary as death results from multifactorial causes. There is a lack of research on the comprehensive analysis of these abnormalities and mortality, especially in Asian countries. Therefore, we aimed to assess the relationship between incidental abnormalities on thoracic CT and mortality in a general screening population using a long-term follow-up analysis.

MATERIAL AND METHODS

Study Design

This retrospective, observational cohort study included participants from an asymptomatic general population who underwent a health check-up at the Center for Health Promotion at the Chonnam National University Hospital. As the primary endpoint of this study was the relationship between incidental abnormalities on screening thoracic CT and long-term mortality, we analyzed participants who underwent thoracic CT and were available for mortality ascertainment with at least a 10-year interval. Therefore, all consecutive health-screening participants (n = 1336) who underwent thoracic CT at our health promotion center between 2007 and 2010 were eligible. Initially, participants aged < 50 years (n = 472) were excluded because of the low prevalence of ILA, as reported in a previous study [13], and participants with a history of cancer (gastric cancer [n = 4], urogenital cancer [n = 3], lung cancer [n = 2], hepatocellular carcinoma [n = 1]), or cardiovascular disease (n = 9) were also excluded. Two of the excluded participants were diagnosed with lung cancer within 6 months of undergoing a health checkup. Participants with poor thoracic CT image quality (n = 3) or missing clinical data (n = 2) were excluded from the study. Figure 1 summarizes the flow of this study, including patient selection. We evaluated the baseline clinical characteristics (age, sex, smoking history with dose, comorbidities, body mass index [BMI], pulmonary function test [PFT] results [forced expiratory volume in one second {FEV_1}, forced vital capacity {FVC}, and FEV_1/FVC ratio], and thoracic CT) of the 840 eligible participants. In addition, lung cancer development was investigated by reviewing electronic medical records.

This study was approved by the Institutional Review Board of the Chonnam National University Hospital (IRB No. CNUH-2022-022). The requirement for informed consent was waived because of the retrospective study design.

Mortality Ascertainment

The study participants were followed up using the Statistics Korea system, which contains statistical information regarding the causes of death of the entire

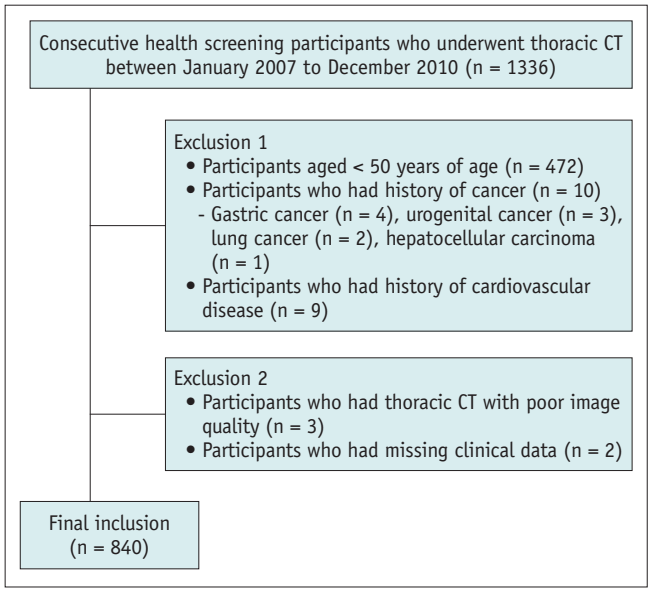

Fig. 1. Study flow diagram.

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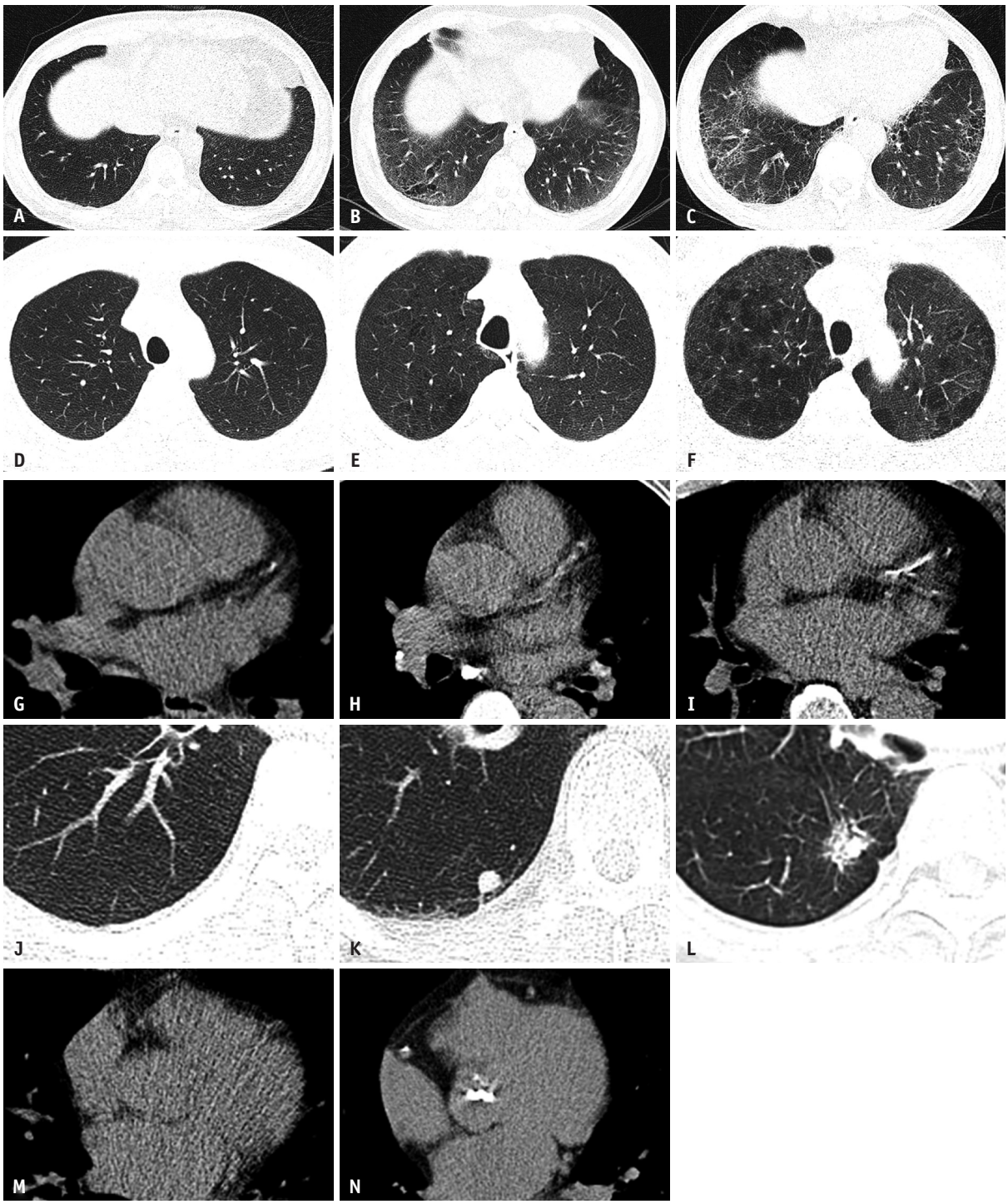

Fig. 2. Representative cases of incidental abnormalities and pulmonary nodules observed on CT.
A-C. Representative cases of ILAs with axial CT images in the lung window setting. **A:** No ILA. **B:** Subpleural ground-glass abnormality and reticulation in both lower lobes, indicating a non-fibrotic ILA. **C:** Subpleural reticulation and traction bronchiectasis with architectural distortion in both lower lobes, indicating a fibrotic ILA. **D-F.** Representative cases of pulmonary emphysema with axial CT images in the lung window setting. **D:** No emphysema. **E:** Centrilobular lucency occupying < 5% of the entire lung (< 5% emphysema). **F:** Centrilobular lucencies occupying ≥ 5% of the entire lung (emphysema ≥ 5%). **G-I.** Representative cases of CAC with axial CT images in the mediastinal window setting. **G:** Mild CAC (Agatston score: 11), **H:** Moderate CAC (Agatston score: 132), **I:** Severe CAC (Agatston score: 1106). **J-L.** Representative cases of pulmonary nodules with axial CT images in the lung window setting. **J:** No pulmonary nodules. **K:** A non-suspicious pulmonary nodule in the right lower lobe with a mean diameter of 7 mm and solid appearance. **L:** A suspicious pulmonary nodule in the right lower lobe with a mean diameter of 16.6 mm and part-solid appearance. **M, N.** Representative cases of AV calcification with axial CT images in the mediastinal window setting. **M:** No AV calcification. **N:** AV calcification. AV = aortic valve, CAC = coronary artery calcification, ILA = interstitial lung abnormality

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Korean population. Information on mortality and causes of death was ascertained at least 10 years after screening, up to December 2020. The causes of death were updated until December 2020 and classified into four different groups based on the International Classification of Diseases (ICD) 10 codes: cancer (ICD10 codes C00–C99), respiratory disease (ICD10 codes J00–J99), cardiovascular disease (ICD10 codes I00–I99), and other causes of death (all remaining ICD10 codes).

Thoracic CT Imaging Protocol and Image Analysis

Thoracic CT was performed using a 16-detector row CT scanner (LightSpeed 16, GE Healthcare) and a 128-detector row CT scanner (Somatom Definition Flash, Siemens Healthineers), without contrast medium injection. The following CT imaging parameters were used: tube voltage, 120 kVp; gantry rotation time, < 0.5 seconds; and a reference tube current of 50 mA with dose modulation. All CT images were reconstructed using standard sharp kernels with a slice thickness of 3–5 mm along the axial plane. Among the 840 scans, 616 (73.3%) and 188 (22.4%) were performed using 3-mm and 3.8-mm slice thicknesses, respectively, while 36 (4.3%) were performed using 5-mm slice thickness.

The thoracic CT images were reviewed by two independent thoracic radiologists (with 7 and 10 years of experience in thoracic CT interpretation, respectively), and consensus was reached for the study analysis. Five CT abnormalities and their subtypes were evaluated, including ILA, emphysema, CAC, pulmonary nodules, and AV calcification (Fig. 2). Inter-reader agreements for the initial readings of CT abnormalities and their subtypes were recorded. If a consensus was not reached, the rating of the senior reader was adopted.

ILA were defined as non-dependent abnormalities affecting > 5% of any lung zone, including ground-glass or reticular abnormalities, architectural distortion, traction bronchiectasis, non-emphysematous cysts, and honeycombing [6]. ILA status was visually categorized into three groups: none, non-fibrotic ILA, and fibrotic ILA (Fig. 2A-C). Fibrotic ILA were defined as evidence of fibrosis, characterized by architectural distortion with traction bronchiectasis or honeycombing. Emphysema was assessed for parenchymal (non-paraseptal) emphysema and graded according to the Fleischner Society visual classification system [7]. Visual emphysema on CT was defined as parenchymal (nonparaseptal) emphysema and categorized into three groups: none, < 5%, and ≥ 5% emphysema of the entire lung, corresponding to mild and moderate emphysema, respectively, according to the Fleischner Society classification system (Fig. 2D-F). CAC was assessed quantitatively by two readers using a dedicated software (TeraRecon, TeraRecon Inc., Durham). The quantitative measurement of Agatston CAC was categorized into four groups: 0, 1–99, 100–300, and > 300 (Fig. 2G-I) [14]. Pulmonary nodules were categorized according to Lung-Reporting and Data System version 1.1 [15]. Nodules corresponding to category 4 were defined as suspicious nodules (Fig. 2J-L). The visual assessment of AV calcification was performed according to the consensus statement from the British Society of Cardiovascular Imaging, British Society of Cardiac Computed Tomography, and the British Society of Thoracic Imaging (Fig. 2M, N) [12].

Statistical Analysis

Statistical analyses were performed using SPSS Ver. 25.0 software (IBM Corp.) and STATA ver. 17.0 software (StataCorp). Statistical assessment of the differences between the groups was performed using Pearson's chi-square test or Fisher's exact test for categorical variables, and a two-tailed *t* test for continuous variables. Inter-reader agreement for incidental CT abnormalities (ILA, emphysema, CAC, and AV calcification) and pulmonary nodules was calculated using the kappa (κ) coefficient. According to the Cohen's κ coefficient, κ < 0.40 was interpreted as poor agreement, 0.41–0.60 as moderate, 0.61–0.80 as substantial, and 0.81–1 as almost perfect agreement. Kaplan–Meier analysis with the log-rank test was performed to assess the relationship between incidental CT abnormalities and all-cause mortality. The z-test was used to compare the 10-year all-cause mortality rates. Univariable and multivariable Cox proportional hazards regression analyses were performed to identify the risk factors for all-cause mortality. Covariates including age, sex, smoking history, BMI, and PFT results were included, along with incidental CT abnormalities. Multivariable competing risk analysis was performed to evaluate the association between incidental CT abnormalities and cause-specific mortality, including deaths specific to non-pulmonary cancer, lung cancer, respiratory disease, and cardiovascular disease. *p* values < 0.05 were considered statistically significant.

RESULTS

Demographics and Baseline Clinical Characteristics

Table 1 presents the baseline demographic and clinical

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Table 1. Demographics and Clinical Characteristics of the Study Participants

Variables	Total (n = 840)
Age, year	58.5 ± 6.7
Sex	
Male	564 (67.1)
Female	276 (32.9)
Smoking history	
Present	449 (53.5)
Never	391 (46.5)
Smoking, pack-years	18.2 ± 20.5
Comorbidities	
Hypertension	197 (23.5)
Diabetes	88 (10.5)
BMI, kg/m^2	23.9 ± 2.9
PFT	
FEV_1/FVC ≤ 0.7	75 (8.9)
FEV_1%predicted	89.7 ± 16.2
FVC%predicted	89.9 ± 14.9
Lung cancer	
Entire follow-up period	12 (1.4)
Follow-up length, year	10.9 ± 1.4 (IQR, 10.4–11.6)

Data are mean ± standard deviation or number of participants with percentage in parentheses unless specified otherwise. BMI = body mass index, FEV_1 = forced expiratory volume in one second, FVC = forced vital capacity, IQR = interquartile range, PFT = pulmonary function test

characteristics of the study population. Among the 840 participants included in the analysis, 564 (67.1%) were male and 276 (32.9%) were female. The mean age was 58.5 years. Overall, 449 participants (53.5%) had a history of smoking, with a mean smoking dose of 18.2 pack-years. A further 88 (10.5%) participants had a history of diabetes and 197 (23.5%) had a history of hypertension. The mean BMI was 23.9 kg/m^2. Seventy-five (8.9%) participants had an FEV_1/FVC ratio ≤ 0.7 or less. Twelve participants (12/840, 1.4%) were diagnosed with lung cancer during the follow-up period. The mean follow-up period was 10.9 years.

The demographic and baseline clinical characteristics of the study population stratified by incidental CT abnormalities are shown in Supplementary Tables 1 and 2. Participants with incidental CT abnormalities (ILA, emphysema, and CAC) were more likely to be older, male, and smokers than those without incidental CT abnormalities ($p < 0.05$). The percentage of participants with an FEV_1/FVC ratio of 0.7 or less was significantly higher among those with ILA, emphysema, and AV calcification than among those without ($p < 0.05$).

CT Analysis

Overall, 55/840 participants (6.5%) were considered

Table 2. Consensus and Inter-Reader Agreement in CT Interpretation

CT Abnormalities	Consensus	Reader 1	Reader 2	Kappa Coefficient
ILA				0.74 (0.65, 0.83)
No ILA	785 (93.5)	784 (93.3)	788 (93.8)	
Non-fibrotic ILA	35 (4.1)	37 (4.4)	33 (3.9)	
Fibrotic ILA	20 (2.4)	19 (2.3)	19 (2.3)	
Emphysema				0.86 (0.82, 0.93)
No emphysema	669 (79.6)	667 (79.4)	686 (81.7)	
< 5% emphysema	141 (16.8)	144 (17.1)	126 (15.0)	
≥ 5% emphysema	30 (3.6)	29 (3.5)	28 (3.3)	
CAC*				0.83 (0.73, 0.81)
No CAC (0)	552 (65.7)	552 (65.7)	553 (65.8)	
Mild CAC (1–99)	208 (24.8)	208 (24.8)	213 (25.4)	
Moderate CAC (100–300)	49 (5.8)	49 (5.8)	65 (7.7)	
Severe CAC (> 300)	31 (3.7)	31 (3.7)	25 (3.0)	
Pulmonary nodule				0.85 (0.81, 0.89)
No nodule	444 (52.8)	448 (53.3)	481 (57.3)	
Non-suspicious nodule	367 (43.7)	363 (43.2)	333 (39.6)	
Suspicious nodule	29 (3.5)	29 (3.5)	26 (3.1)	
AV calcification				0.82 (0.76, 0.88)
No AV calcification	743 (88.5)	744 (88.6)	746 (88.8)	
AV calcification	97 (11.5)	96 (11.4)	94 (11.2)	

Data are number of participants with percentage in parentheses. *The CAC consensus result was based on the quantitative measurement of the reader 1. AV = aortic valve, CAC = coronary artery calcification, ILA = interstitial lung abnormality

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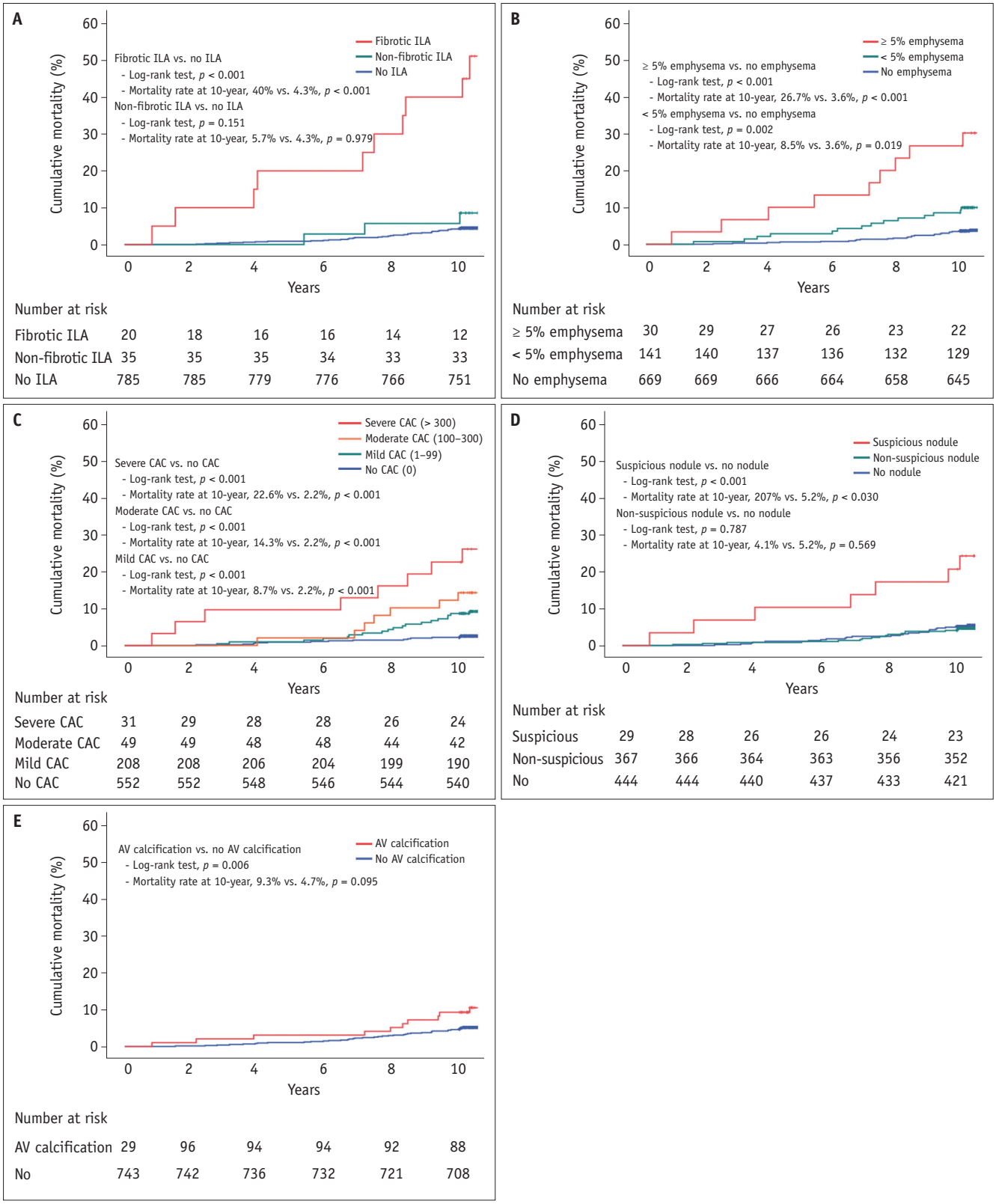

Fig. 3. Kaplan–Meier curves of all-cause mortality according to incidental CT abnormalities and pulmonary nodule.
A. Kaplan–Meier curves of cumulative mortality according to ILA. **B.** Kaplan–Meier curves of cumulative mortality according to pulmonary emphysema. **C.** Kaplan–Meier curves of cumulative mortality according to CAC. **D.** Kaplan–Meier curves of cumulative mortality according to pulmonary nodule. **E.** Kaplan–Meier curves of cumulative mortality according to AV calcification. AV = aortic valve, CAC = coronary artery calcification, ILA = interstitial lung abnormality

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to have an ILA, 20/840 (2.4%) were classified as having fibrotic ILA, 35/840 (4.1%) were classified as non-fibrotic ILA. Among the 171 participants (171/840, 20.4%) with emphysema, 30 (3.6%) were classified as having ≥ 5% emphysema. Severe, moderate, and mild CAC were present in 3.7% (31/840), 5.8% (49/840), and 24.8% (208/840) of participants, respectively, among those presenting with CAC (288/840, 34.3%). Pulmonary nodules were present in 396 participants (396/840, 47.2%) and suspicious pulmonary nodules were present in 29 participants (29/840, 3.5%). Five participants (5/29, 17.2%) with suspected pulmonary nodules were eventually diagnosed with lung cancer. AV calcification was observed in 97 participants (97/840, 11.5%). All CT abnormalities, except for ILA, demonstrated excellent inter-reader agreement ($\kappa > 0.8$). The two readers showed substantial agreement for ILA ($\kappa = 0.74$) (Table 2).

Relationship between Incidental CT Abnormalities and All-Cause Mortality

The 10-year all-cause mortality was significantly higher among participants with fibrotic ILA (40% vs. 4.3%, $p < 0.001$), ≥ 5% emphysema (26.7% vs. 3.6%, $p < 0.001$), < 5% emphysema (8.5% vs. 3.6%, $p = 0.002$), severe CAC (22.6% vs. 2.2%, $p < 0.001$), moderate CAC (14.3% vs. 2.2%, $p < 0.001$), mild CAC (8.7% vs. 2.2%, $p < 0.001$), and suspicious pulmonary nodules (20.7% vs. 5.2%, $p = 0.030$) than among those without ILA, emphysema, CAC, and pulmonary nodules, respectively. The all-cause mortality during the entire follow-up period was significantly higher among participants with fibrotic ILA ($p < 0.001$), ≥ 5% emphysema ($p < 0.001$), < 5% emphysema ($p = 0.002$), mild/moderate/severe CAC (all $p < 0.001$), suspicious pulmonary nodules ($p < 0.001$), and AV calcification ($p = 0.006$) as compared to those without ILA, emphysema, CAC, pulmonary nodules, and AV calcification, respectively (Fig. 3).

All incidental CT abnormalities were significantly associated with increased all-cause mortality in univariable Cox proportional hazards regression (all $p < 0.001$). However, multivariable Cox proportional hazards regression revealed that fibrotic ILA was independently associated with increased all-cause mortality compared with no ILA (hazard ratio [HR], 2.52; 95% confidence interval [CI], 1.02–6.22, $p = 0.046$) (Table 3).

Table 3. Cox Proportional Hazards Regression for All-Cause Mortality (n = 57)

Variables	Univariable Analysis		Multivariable Analysis	
	Unadjusted HR (95% CI)	*P*	Adjusted HR* (95% CI)	*P*
ILA				
No ILA	Reference		Reference	
Non-fibrotic ILA	2.10 (0.75–5.86)	0.157	1.05 (0.36–3.10)	0.932
Fibrotic ILA	14.06 (7.23–27.34)	< 0.001	2.52 (1.02–6.22)	0.046
Emphysema				
No emphysema	Reference		Reference	
< 5% emphysema	2.53 (1.38–4.62)	0.003	1.77 (0.87–3.60)	0.114
≥ 5% emphysema	8.96 (4.39–18.29)	< 0.001	1.46 (0.47–4.51)	0.515
CAC†				
No CAC (0)	Reference		Reference	
Mild CAC (1–99)	3.12 (1.69–5.77)	< 0.001	1.88 (0.97–3.67)	0.063
Moderate CAC (100–300)	4.95 (2.17–11.30)	< 0.001	2.19 (0.88–5.47)	0.093
Severe CAC (> 300)	8.74 (3.82–19.98)	< 0.001	2.14 (0.76–6.00)	0.148
Pulmonary nodule				
No nodule	Reference		Reference	
Non-suspicious nodule	1.08 (0.62–1.88)	0.796	0.82 (0.51–1.63)	0.767
Suspicious nodule	4.94 (2.15–11.38)	< 0.001	1.74 (0.63–4.81)	0.284
AV calcification				
No AV calcification	Reference		Reference	
AV calcification	2.32 (1.25–4.30)	0.008	0.85 (0.43–1.69)	0.641

*Multivariable Cox regression models were adjusted for age, sex, smoking status, FEV_1/FVC ratio, and body mass index, †The CAC result was based on the Agatston score using the dedicated software. AV = aortic valve, CAC = coronary artery calcification, CI = confidence interval, FEV_1 = forced expiratory volume in one second, FVC = forced vital capacity, HR = hazard ratio, ILA = interstitial lung abnormality

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Relationship between Incidental CT Abnormalities and Cause-Specific Mortality

The most common cause of death was cancer, accounting for 51% (29/57) of the study population, of which 14% (8/57) were lung cancer-related and 37% (21/57) were non-pulmonary cancer-related. Lung cancer is the most common cause of cancer-related death. Nine participants (9/57, 16%) died due to respiratory disease and three participants (3/57, 5.3%) died due to cardiovascular disease. Participants with incidental CT abnormalities showed higher all-cause mortality than those without incidental CT abnormalities. In particular, lung cancer-related deaths (20% vs. 12%) and respiratory disease-related deaths (40% vs. 7.1%) were observed more frequently among participants with ILA (Table 4, Supplementary Table 3).

ILA were independently associated with increased cause-specific mortality from lung cancer or respiratory disease (subdistribution HR [sHR], 6.22 [95% CI, 1.64–23.58], $p = 0.007$), and emphysema was found to be independently associated with increased cause-specific mortality from non-pulmonary cancers (sHR, 3.55 [95% CI, 1.42–8.87], $p = 0.007$) in a competing risk analysis using multivariable Cox proportional hazards regression (Table 5).

DISCUSSION

The primary findings of this study can be summarized as follows: 1) incidental CT abnormalities (fibrotic ILA, all degrees of emphysema and CAC, and AV calcification) and suspicious pulmonary nodules were all significantly associated with increased all-cause mortality in the general screening population, 2) multivariable Cox proportional hazards regression revealed that only fibrotic ILA was independently associated with increased all-cause mortality, and 3) ILA was a specific risk factor for lung cancer and respiratory disease-related deaths on competing risk analysis.

ILA is an important incidental abnormality detected on thoracic CT which is associated with higher mortality [16]. The prevalence of ILA in our study was 6.6%, similar to that reported in previous population-based cohort studies [6]. Since ILA lies within the spectrum of pulmonary fibrosis, appropriate management is recommended in these groups to avoid the development of IPF and poor respiratory events [17]. Chae et al. [18] recently investigated the radiologic-pathologic correlation of ILA and concluded that fibrotic ILA frequently exhibited a pathologic usual interstitial pneumonia pattern, and were significantly associated

Table 4. Cause of Death according to Incidental CT Abnormalities and Pulmonary Nodule

Variables	Total (n = 840)	ILA		Emphysema		CAC		Pulmonary Nodule		AV Calcification	
		No (n = 785)	Yes (n = 55)	No (n = 669)	Yes (n = 171)	No (n = 552)	Yes (n = 288)	No (n = 444)	Yes (n = 396)	No (n = 743)	Yes (n = 97)
Total deaths, %	57 (6.8)	42 (5.4)	15 (27)	31 (4.6)	26 (15)	19 (3.4)	38 (13)	27 (6.1)	30 (7.6)	44 (5.9)	13 (13)
Cause of deaths, %											
Cancer*	29 (51)	23 (55)	6 (40)	15 (48)	14 (54)	12 (63)	17 (45)	14 (52)	15 (50)	23 (52)	6 (46)
Lung cancer†	8 (14)	5 (12)	3 (20)	3 (9.7)	5 (19)	3 (16)	5 (13)	2 (7.4)	6 (20)	6 (14)	2 (15)
Non-pulmonary cancer†	21 (37)	18 (43)	3 (20)	12 (39)	9 (35)	9 (47)	12 (32)	12 (44)	9 (30)	17 (39)	4 (31)
Respiratory disease§	9 (16)	3 (7.1)	6 (40)	4 (13)	5 (19)	3 (16)	6 (16)	5 (19)	4 (13)	7 (16)	2 (15)
Cardiovascular disease‖	3 (5.3)	3 (7.1)	0 (0)	1 (3.2)	2 (7.7)	1 (5.3)	2 (5.3)	2 (7.4)	1 (3.3)	2 (4.5)	1 (7.7)
Other causes¶	16 (28)	13 (31)	3 (20)	11 (36)	5 (7.7)	3 (16)	13 (34)	6 (22)	10 (33)	12 (27)	4 (31)

Data are number of participants with percentage in parentheses. *Cancer deaths included the following: ICD 10 codes C00–C99, †Lung cancer death included ICD 10 code C34, ‡Non-pulmonary cancer death included ICD 10 codes C00-C99 excluding C34, §Respiratory disease death included ICD10 codes J00–J99, ‖Cardiovascular disease death included ICD 10 codes I00–I99, ¶Other causes of death included all remaining ICD 10 codes including certain infectious and parasitic diseases (A00–B99), diseases of the nervous system (G00–G99), diseases of the digestive (K00–K95), diseases of the genitourinary system (N00–N99), and symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified (R00–R99). AV = aortic valve, CAC = coronary artery calcification, ICD = International Classification of Disease, ILA = interstitial lung abnormality

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Table 5. Competing Risk Analysis of Cause-Specific Mortality according to Incidental CT Abnormalities and Pulmonary Nodule

CT Abnormalities	Cause of Mortality					
	Non-Pulmonary Cancer (n = 21)		Lung Cancer or Respiratory Disease (n = 18)		Cardiovascular Disease (n = 3)	
	sHR* (95% CI)	*P*	sHR* (95% CI)	*P*	sHR* (95% CI)	*P*
ILA	0.67 (0.19–2.39)	0.540	6.22 (1.64–23.58)	0.007	N/A	N/A
Emphysema	3.55 (1.42–8.87)	0.007	1.44 (0.47–4.45)	0.530	3.89 (0.34–45.09)	0.280
CAC	1.39 (0.57–3.40)	0.470	1.37 (0.46–4.13)	0.570	2.48 (0.31–20.12)	0.400
Pulmonary nodule	0.58 (0.25–1.37)	0.210	1.30 (0.49–3.43)	0.600	0.57 (0.05–6.95)	0.660
AV calcification	0.85 (0.24–3.04)	0.940	1.11 (0.27–4.58)	0.880	4.81 (0.34–68.45)	0.250

*Multivariable competing risk Cox hazard models were adjusted for age, sex, smoking status, FEV_1/FVC, and body mass index. AV = aortic valve, CAC = coronary artery calcification, CI = confidence interval, FEV_1 = forced expiratory volume in one second, FVC = forced vital capacity, ILA = interstitial lung abnormality, N/A = not available, sHR = subdistribution hazard ratio

with higher mortality. Since fibrotic ILA is an important early precursor of IPF [6], which has been associated with a gradual increase in IPF morbidity and mortality [19], fibrotic ILA may be an independent predictor of long-term mortality among incidental CT abnormalities in our study. Furthermore, our study showed that ILA is a specific risk factor for lung cancer or respiratory disease-related deaths. The association between fibrotic ILA and higher mortality may be partially explained by the higher mortality from lung cancer. Axelsson et al. [20] also reported that ILA with fibrosis imaging patterns were significantly associated with lung cancer-related deaths compared to no ILA, whereas ILA was not associated with mortality from cancers other than lung cancer.

Our study also reflects the current medical environment in South Korea. Among the Organization for Economic Cooperation and Development countries, Korea has a higher than average age-adjusted death rate (79.3 per 100000 population) from respiratory diseases, whereas its age-adjusted death rate from cardiovascular disease is the lowest among these countries [21]. The incidence and mortality rates of IPF in Korea are increasing, similar to those in Western countries. Ko et al. [22] reported that patients with IPF had significantly higher all-cause and cause-specific mortality rates than those without IPF. Emphysema is an important form of COPD [23] which, along with COPD, is associated with increased long-term mortality of any severity [24]. In our study, emphysema showed a statistically significant effect on long-term all-cause mortality only in univariable analysis. Our study found that the effect of CAC on all-cause mortality was less significant, which may be related to the trend of decreasing mortality due to acute myocardial infarction in Korea owing to timely diagnosis and early intervention [25]. Cancer is the most common cause of death worldwide, with lung cancer accounting for the highest number of cancer-related deaths in our study. These results are consistent with cancer statistics in Korea [26]. Suspicious pulmonary nodules were significantly associated with increased all-cause mortality in the Kaplan?Meier analysis with the log-rank test. The higher prevalence of lung cancer among suspicious nodules may have resulted in increased all-cause mortality. Nonetheless, suspicious nodules were not identified as an independent risk factor for all-cause mortality in the multivariable Cox proportional hazards regression analysis.

The American College of Radiology recommends that incidental abnormalities on lung cancer screening CT be routinely reported [27]. Our study revealed that ILA, emphysema, CAC, and AV calcification were all associated with long-term all-cause mortality; thus, radiologists should consider the clinical implications of these incidental abnormalities and report them to clinicians. Appropriate management is definitively required in patients with fibrotic ILA, as they are associated with long-term mortality, along other incidental abnormalities. The Fleischner Society recommends active monitoring of patients with ILA to assess the risk of progression [6]. Radiological features of fibrotic ILA are risk factors for progression. Risk factor reduction and clinical reassessment with repeat PFTs every 3–12 months are recommended for patients with fibrotic ILA. A follow-up CT is recommended at 12–24 months; however, it should be performed sooner if clinical or physiological progression is suspected.

Our study has several limitations. Firstly, this was a retrospective single-center study. Nationwide or multinational studies are needed to apply these results to evidence-based medicine. Moreover, since only participants who underwent initial CT more than 10 years ago were

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included in the study for long-term survival analysis, thin cross-sectional images were not available, which may have limited the evaluation of CT abnormalities. Nonetheless, the two radiologists showed good inter-reader agreement for each incidental abnormality. Finally, we did not use a quantitative method for the emphysema index due to the inherent limitation of thin cross-sectional images; therefore, further quantitative analyses are needed to determine the objectivity and reproducibility of our results.

In conclusion, incidental abnormalities on thoracic CT screening were associated with increased all-cause mortality during long-term follow-up. Among incidental CT abnormalities, fibrotic ILA were independently associated with increased mortality. Appropriate management and surveillance may be required for patients with fibrotic ILA on thoracic CT obtained for general screening purposes.

Supplement

The Supplement is available with this article at https://doi.org/10.3348/kjr.2022.0131.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Jong Eun Lee, Won Gi Jeong. Data curation: Jong Eun Lee. Formal analysis: Jong Eun Lee, Won Gi Jeong. Investigation: Jong Eun Lee. Methodology: Jong Eun Lee, Won Gi Jeong, Kum Ju Chae, Yeon Joo Jeong. Project administration: Jong Eun Lee, Won Gi Jeong. Software: Jong Eun Lee. Supervision: Won Gi Jeong. Validation: Jong Eun Lee. Visualization: Jong Eun Lee. Writing—original draft: Jong Eun Lee, Won Gi Jeong. Writing—review & editing: all authors.

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