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Cardiovascular disease prediction: do pulmonary disease-related chest CT features have added value?

Pushpa M. Jairam · Pim A. de Jong · Willem P. Th. M. Mali · Ivana Isgum · Yolanda van der Graaf · on behalf of the PROVIDI study-group

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Abstract

Objective Certain pulmonary diseases are associated with cardiovascular disease (CVD). Therefore we investigated the incremental predictive value of pulmonary, mediastinal and pleural features over cardiovascular imaging findings.

Methods A total of 10,410 patients underwent diagnostic chest CT for non-cardiovascular indications. Using a case-cohort approach, we visually graded CTs from the cases and from an approximately 10 % random sample of the baseline cohort (n=1,203) for cardiovascular, pulmonary, mediastinal and pleural findings. The incremental value of pulmonary disease-related CT findings above cardiovascular imaging findings in cardiovascular event risk prediction was quantified by comparing discrimination and reclassification.

Results During a mean follow-up of 3.7 years (max. 7.0 years), 1,148 CVD events (cases) were identified. Addition of pulmonary, mediastinal and pleural features to a cardiovascular imaging findings-based prediction model led to marginal improvement of discrimination (increase in c-index from 0.72 (95 % CI 0.71–0.74) to 0.74 (95 % CI 0.72–0.75)) and reclassification measures (net reclassification index 6.5 % (p<0.01)).

Conclusion Pulmonary, mediastinal and pleural features have limited predictive value in the identification of subjects at high risk of CVD events beyond cardiovascular findings on diagnostic chest CT scans.

Key Points

- *Incidental cardiovascular findings on routine chest CT can predict cardiovascular disease*
- *Non-cardiovascular chest CT abnormalities are associated with cardiovascular disease*
- *Non-cardiovascular chest CT features have limited predictive value beyond cardiovascular features*

Keywords Chest CT imaging · CVD risk prediction · Pulmonary disease-related CT findings · Cardiovascular imaging · Cardiovascular disease

Introduction

Chest computed tomography (CT) has emerged as a commonly used imaging modality in the evaluation of thoracic diseases, with more than 10 million chest CTs performed annually in the USA [1, 2]. In addition to the clinically valuable information embedded in the imaging findings related to the chest CT indication, incidental findings that are unsuspected or unrelated to the indication contain prognostically valuable information about multiple diseases [3–5]. In fact, in the case of incidental cardiovascular CT features, such as coronary and extracoronary calcifications, cardiovascular disease (CVD) risk can immediately be derived from these markers of organ damage visible on CT [6–11].

An explorative study [12] has proposed a different approach for CVD risk prediction strictly based on information readily available to the radiologist. The provided prediction rule allows one to calculate up to 5-year predicted probabilities for non-fatal and fatal CVD events by combining age,

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P. M. Jairam (✉) · Y. van der Graaf
Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands
e-mail: pjairam@umcutrecht.nl

P. M. Jairam · P. A. de Jong · W. P. T. M. Mali
Department of Radiology, University Medical Center Utrecht, Utrecht, The Netherlands

I. Isgum
Image Sciences Institute, University Medical Center Utrecht, Utrecht, The Netherlands

gender, CT indication, cardiac diameter, left anterior descending coronary artery calcifications, mitral valve calcifications and descending aorta calcifications. Addressing conventional risk factors is not possible in daily routine practice, since this information is in general not available to the radiologist. Moreover, risk factor detection, earlier in the disease process, precedes in many patients the presence of the image findings. Additionally, a substantial proportion of CVD events occur in individuals without conventional risk factors or in subjects with yet undetected or underdiagnosed risk factors [13]. There are several studies supporting a shift in CVD risk assessment from conventional risk factors, as they are merely a surrogate for atherosclerosis, to direct measures of subclinical atherosclerosis [13–15]. Utilization of markers of subclinical target organ damage for CVD risk prediction, like cardiovascular CT features incorporated in the imaging-based model, provide a novel strategy and adequate estimation of CVD risk irrespective of the conventional risk factor status.

Emerging data indicate a direct link between certain pulmonary diseases and cardiovascular disease. Mechanisms such as ongoing pulmonary inflammation, repair mechanisms, misbalances between proteases and anti-proteases and autoimmune phenomena have been suggested to explain the relationship between pulmonary diseases and cardiovascular disease. Additionally, chest CT abnormalities reflecting these pulmonary diseases, e.g. airway thickening, pulmonary ground glass opacity, pulmonary consolidation, pleural effusion and mediastinal lymphadenopathy, were found to be associated with CVD [16–19]. Whether these pulmonary, mediastinal and pleural characteristics, which can be evaluated in the same image as the cardiovascular findings without additional examining or radiation exposure, improve CVD risk estimation beyond what is possible with cardiovascular findings is unknown. To address this issue we evaluated the incremental predictive value of pulmonary, mediastinal and pleural findings on routine diagnostic chest CT over a cardiovascular CT features-based prediction model.

Materials and methods

Study population

This is an ancillary study of the PROgnostic Value of unrequested Information in Diagnostic Imaging (PROVIDI) study. The PROVIDI study was conceived from the perspective of the radiologists, to determine the prognostic relevance of the growing amount of uncertain incidental findings. Only information readily available to the radiologist is addressed in this study. Since in general, other risk factors besides age and gender are not easy accessible for the radiologist, we could not provide information on the distribution of these other risk factors in the current study. This study was approved by the ethical review board of the University Medical Center Utrecht (number 06/193); informed consent was waived because a privacy protocol was implemented in the study protocol.

The rationale and design of the PROVIDI study has been described in detail [4]. Briefly, the study population comprised 23,443 subjects aged 40 years and over who underwent routine clinical chest CT imaging between 2002 and 2005 for various diagnostic clinical indications in participating hospitals in the Netherlands. Patients with a diagnosis of primary lung cancer (including mesothelioma) or distant metastatic disease from other types of cancer (excluding hematologic malignancies) at baseline were excluded (n=9,077), because of the poor prognosis. Also excluded were patients yielding prior history of CVD or subjects with a CT referral indication directly related to (suspected) cardiovascular pathology (n= 2,303), to ensure that the evaluated calcifications were truly "incidental".

Sample selection and study design

In the present study, 10,410 participants represent the full study cohort and were considered for analyses. Subjects who developed a CVD event during follow-up were identified as cases. We used a case-cohort approach as introduced by Prentice [20], using all cases and an approximately 10 % random sample from the full study cohort (subcohort) at the beginning of the study. With sampling fractions of at least 0.10, results of a case-cohort analysis are similar to the full study cohort analysis [21]. The cases together with the subcohort define the study population in which the imaging characteristics are determined. The advantage of this design is that it enables survival analyses without the need to score the chest CT images from the full study cohort. Figure 1 shows a flowchart of the study design and the selection of cases and subcohort.

Scoring of CT characteristics

All chest CT examinations were obtained between January 2002 and December 2005, using multi-detector CT (2–64 detector rows) from different vendors according to the prevailing routine clinical protocols of the participating hospitals. All types of CT (including non-contrast and non-triggered) protocols were considered eligible as long as the field of view included the heart and full length of the thoracic aorta. Section thicknesses varied according to the chest CT indication and corresponding protocol.

CT examinations were examined for left anterior descending (LAD) coronary artery calcifications, mitral valve calcifications, descending aorta calcifications and cardiac diameter. This set of four cardiovascular CT features enabled adequate identification of subjects at high risk of CVD [12]. Additionally, CT images were evaluated for airway thickening, ground

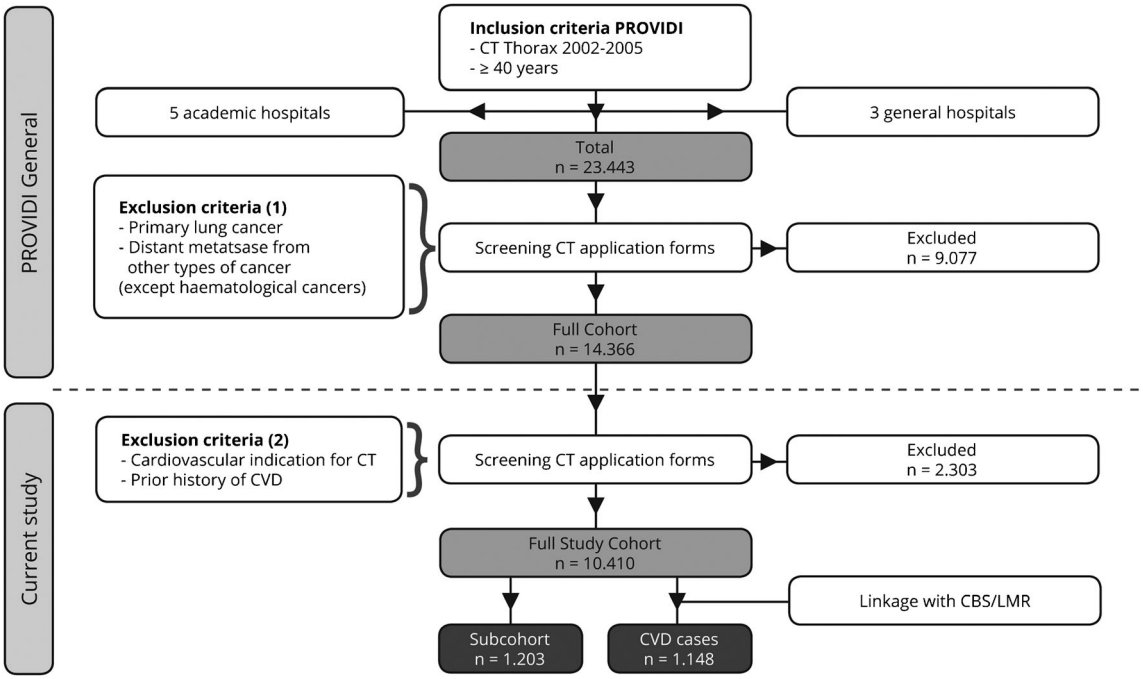

Fig. 1 Flowchart of study design. *CBS* Central Bureau of Statistics, *LMR* Dutch medical data registration

glass, consolidation, pleural effusion and mediastinal lymph node diameter. These five pulmonary disease-related CT findings have been previously shown to be associated with future CVD events [19]. The presence and extent of the cardiovascular and pulmonary CT abnormalities were graded using a validated simple ordinal [22] (Table 1). Extensive information about the definitions and grading of the CT features can be found in the Electronic Supplementary Material and examples in Fig. 2.

Follow-up and cardiovascular events

CVD events were defined as all coronary events (myocardial infarction, coronary death, coronary insufficiency and angina), cerebrovascular events (ischaemic stroke, haemorrhagic stroke and transient ischaemic attack), peripheral artery disease (intermittent claudication) and heart failure. Data on fatal and non-fatal CVD events were obtained from the Dutch National Registry of Hospital Discharge Diagnoses and the National Death Registry. This registry assigns a code to each non-fatal and fatal CVD event, according to the International Classification of Diseases, 9th and10th Revision (ICD-9 and ICD-10); details are shown in the Electronic Supplementary Material. The database was linked to the study cohort with a validated probabilistic method [23, 24]. As previously demonstrated, the overall quality of Dutch national registers is high and ICD codes have high sensitivities and positive predictive values [25, 26], enabling reliable identification of cases and follow-up. Whenever multiple events occurred, the first event was taken as an end point.

Statistical analyses

Baseline characteristics and chest CT findings were summarized for the subcohort and the cases. Quantitative data were described with median (interquartile range) because of their abnormal distribution. Qualitative data were described using percentages. To compare subjects within the subcohort and patients who experienced a CVD event, differences in continuous variables were analysed with Mann–Whitney *U* test. Differences in categorical variables were tested using chi-square tests. The analysis comprised three stages. The first was an assessment of the associations between each pulmonary disease-related CT finding and future CVD events; the second involved the derivation of a cardiopulmonary CT features prediction rule consisting of the four graded cardiovascular CT features, plus a selection of pulmonary disease-related CT findings (a forward stepwise procedure was used for predictor selection) and the third involved comparison of discrimination and reclassification between the cardiopulmonary CT features model and the model only based on cardiovascular CT features. For a more detailed statistical description, see the Electronic Supplementary Material. Analyses were performed with R-project software package, version 2.15 (www.r-project.org).

Table 1 Semi-quantitative grading score of various cardiovascular and pulmonary disease-related CT findings on chest CT

	0=Absent	1=Mild	2=Moderate	3=Severe
LAD coronary artery calcifications				
Number and size of calcifications	None	1–2 focal limited to ≤2 slices	>2 focal or 1 extending >2 slices	Fully calcified coronary artery extending multiple slices
Descending aorta calcifications				
Number and size of calcifications	None	≤3 focal	4–5 focal or 1 extending ≥3 slices	>5 focal or >1 extending ≥3 slices
Mitral valve calcifications				
Number of affected valve leaflet(s)	None	1 leaflet	2 leaflets	
Airway thickening				
Number of affected lobes (range 0–5)	0	1	2	≥3
Consolidation				
Number of affected lobes (range 0–5)	0	1	2	≥3
Ground glass				
Number of affected lobes (range 0–5)	0	1	2	≥3
Pleural effusion				
Sum of left and right fluid layers thickness on axial images, cm	0	<6	6–12	>12
Lymph node				
Short axis diameter of the largest lymph node, mm	<6	6–10	>10	

LAD left anterior descending

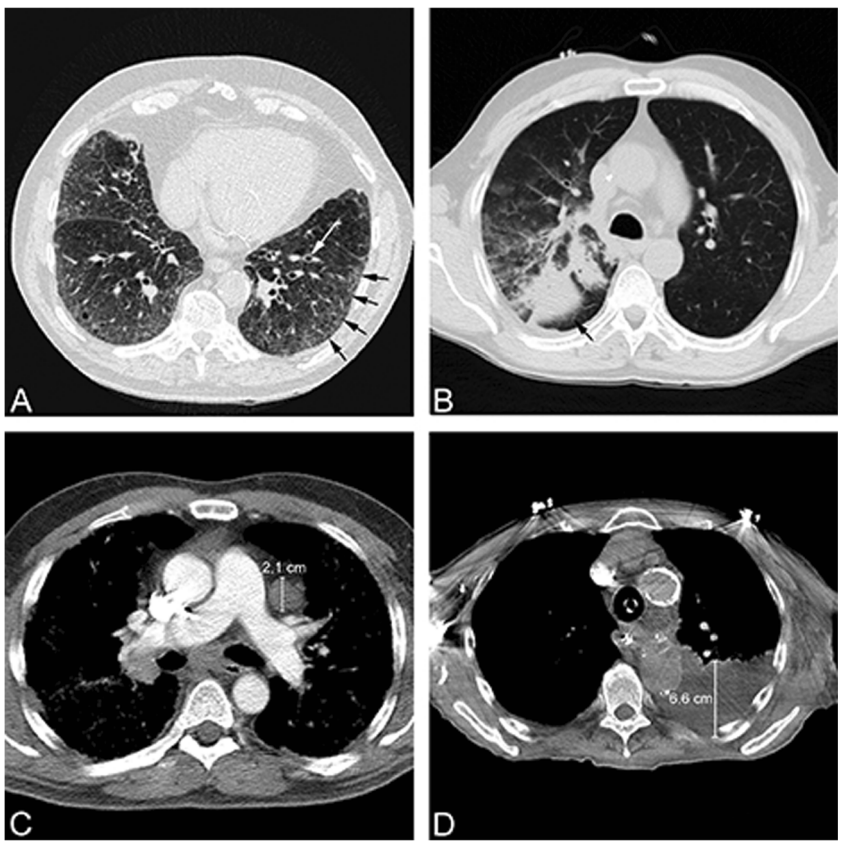

Fig. 2 Examples of pulmonary, mediastinal and pleural CT imaging characteristics. **a** Airway thickening (*white arrow*) and ground glass in the left lower lobe (*black arrows*). **b** Consolidation in the right under lobe (*black arrow*). **c** Short axis diameter measurement of the largest mediastinal lymph node. **d** Pleural effusion measurement of left-sided fluid layer on axial image

Results

During a median follow-up of 3.7 years (range 3.2–7.0 years), 1,148 CVD events occurred among the 10,410 subjects of the baseline cohort. Table 2 presents the baseline characteristics and chest CT imaging findings for the subcohort and CVD cases. As expected, the cases were slightly older, more often male and had more numerous and more severe cardiovascular calcifications as well as pulmonary, mediastinal and pleural abnormalities compared to the subcohort. These differences were all statistically significant ($p<0.05$).

In Table 3, unadjusted and adjusted hazard ratios (HRs) and their 95 % confidence intervals (CIs) for CVD events are presented for the mild, moderate and severe categories of airway thickening, ground glass, consolidation, pleural effusion as well as lymph node diameter compared with the absent category. All five pulmonary, mediastinal and pleural findings were significantly related to CVD risk in the age- and sex-adjusted analysis. When estimates were fully adjusted for age, gender, CT indication, LAD coronary artery calcifications, mitral valve calcifications and descending aorta calcifications and cardiac diameter, the association between airway thickening and consolidations with CVD events was no longer significant. Pulmonary, mediastinal and pleural findings that were independently related to future CVD events after accounting for the predictors included in the cardiovascular CT features-based model were ground glass, pleural effusion and lymph node diameter. The HRs for comparison of the severe versus the absent category for these CT features were as follows: ground glass, HR 2.0 (95 % CI 1.6–2.4); pleural effusion, HR 1.7 (95 % CI 1.3–2.2) and lymph node diameter, HR 1.5 (95 % CI 1.3–1.8) (Fig. 3).

To assess the incremental value of pulmonary disease-related CT features over cardiovascular imaging findings, first a Cox proportional hazard model including limited patient characteristics and cardiovascular CT findings was prespecified. This model will further be referred to as the "cardiovascular CT features model" and comprised the following predictors: age, gender, CT indication, cardiac diameter, LAD coronary artery calcifications, mitral valve calcifications and descending aorta calcifications. Second, a "cardiopulmonary CT features model" was derived, adding the three strongest and independent predictors by Cox proportional hazard models of single pulmonary disease-related CT features with future CVD events (ground glass, pleural effusion and lymphadenopathy) to the cardiovascular CT features model. The same selection of the best predictors was obtained with the use of a forward stepwise procedure, for details see the Electronic Supplementary Material.

Addition of ground glass, pleural effusion and lymph node diameter to the cardiovascular CT features model led to marginal improvement of discrimination and reclassification measures (Table 4). Discrimination, expressed by the c-index, increased from 0.72 (95 % CI 0.71–0.74) to 0.74 (95 % CI 0.72–0.75). Reclassification as measured by the net

Table 2 Baseline characteristics and chest CT imaging findings for subjects in the subcohort (n=1,203) and for the cardiovascular disease cases (n=1,148)

	Subcohort n=1,203	CVD cases n=1,148
Age, years	61 (52–71)	68 (59–75)
Male gender, *n* (%)	698 (58)	723 (63)
CT indication, *n* (%)		
Pulmonary disease	457 (38)	505 (44)
Haematological malignancy	132 (11)	80 (7)
Mediastinal disease	132 (11)	103 (9)
Rules out lung cancer	277 (23)	241 (21)
Pulmonary embolism	72 (6)	80 (7)
Other	144 (12)	126 (11)
LAD coronary artery calcifications, *n* (%)		
Mild	373 (31)	298 (26)
Moderate	229 (19)	321 (28)
Severe	120 (10)	207 (18)
Descending aorta calcifications, *n* (%)		
Mild	325 (27)	333 (29)
Moderate	180 (15)	253 (22)
Severe	72 (6)	195 (17)
Mitral valve calcification, *n* (%)		
1 leaflet	84 (7)	149 (13)
2 leaflets	12 (1)	34 (3)
Cardiac diameter, mm	125 (115–134)	130 (121–141)
Airway thickening, *n* (%)		
Mild	120 (10)	138 (12)
Moderate	132 (11)	161 (14)
Severe	108 (9)	138 (12)
Ground glass, *n* (%)		
Mild	144 (12)	172 (15)
Moderate	84 (7)	149 (13)
Severe	96 (8)	138 (12)
Consolidation, *n* (%)		
Mild	180 (15)	184 (16)
Moderate	108 (9)	126 (11)
Severe	48 (4)	57 (5)
Pleural effusion, *n* (%)		
Mild	60 (5)	57 (5)
Moderate	72 (6)	115 (10)
Severe	48 (4)	92 (8)
Lymph node diameter, *n* (%)		
6–10 mm	457 (38)	551 (48)
>10 mm	252 (21)	287 (25)

Values are mean±standard deviation, median (interquartile range) or *n* (%)

LAD left anterior descending

Table 3 Hazard ratios (95 % CI) for cardiovascular events (n=1,148) during a median follow-up period time of 3.7 years according to the pulmonary disease-related CT findings on routine chest CT

	Sex- and age-adjusted HR (95 % CI)	Multivariable[a] adjusted HR (95 % CI)
Airway thickening (%)		
Absent	Reference	Reference
Mild	1.3 (1.3–1.5)	1.0 (0.8–1.3)
Moderate	1.3 (1.1–1.5)	1.2 (1.0–1.4)
Severe	1.4 (1.1–1.7)	1.1 (0.9–1.3)
Consolidation (%)		
Absent	Reference	Reference
Mild	1.1 (0.9–1.3)	0.9 (0.7–1.1)
Moderate	1.5 (1.2–1.8)	1.2 (1.0–1.5)
Severe	1.5 (1.1–1.9)	1.3 (1.0–1.7)
Ground glass (%)		
Absent	Reference	Reference
Mild	1.4 (1.2–1.7)	1.6 (1.3–1.8)
Moderate	1.9 (1.4–2.6)	2.0 (1.7–2.4)
Severe	2.2 (1.6–3.0)	2.0 (1.6–2.4)
Pleural effusion (%)		
Absent	Reference	Reference
Mild	1.3 (1.0–1.7)	1.0 (0.8–1.3)
Moderate	2.7 (1.8–4.0)	1.7 (1.4–2.2)
Severe	2.3 (1.5–3.5)	1.7 (1.3–2.2)
Lymph node diameter (mm)		
<6	Reference	Reference
6–10	1.8 (1.5–2.0)	1.5 (1.3–1.8)
>10	1.9 (1.6–2.2)	1.5 (1.3–1.8)

[a] Multivariable adjusted = adjustment for predictors of the cardiovascular CT features model: age, gender, CT indication, left anterior descending coronary artery calcification, mitral valve calcification, descending aortic calcification and the cardiac diameter

reclassification improvement (NRI) was 6.5 % (P<0.01). This indicates that with the cardiopulmonary CT features model 6.5 % of the subjects are more appropriately reclassified compared with the cardiovascular CT features model, with 0 % improvement in cases and 6.5 % in noncases.

Discussion

In this case-cohort study of 10,410 subjects who underwent routine clinical chest CT scanning, the incremental value of pulmonary, mediastinal and pleural findings over certain cardiovascular characteristics in CVD event risk prediction was evaluated. Ground glass, pleural effusion and lymphadenopathy were associated with an increased risk of CVD events, independent of age, gender, CT indication, cardiac diameter, LAD coronary artery calcifications, mitral valve calcifications and descending aorta calcifications. However, improvement of CVD event risk prediction beyond cardiovascular imaging findings with addition of these three pulmonary, mediastinal and pleural imaging features was only marginal. Thus, incidental vascular calcifications alone offer an important opportunity to identify patients at high risk of cardiovascular disease. Therefore we recommend to routinely report these findings to allow further work-up and/or preventative treatment. This can be an efficient strategy to effectuate a further decline of the global cardiovascular disease burden without providing additional radiation to the patient or increasing health-care costs. However, in many institutions, there still is a controversy among radiologists whether incidental findings should be reported. Correspondingly, a professional consensus about standardized and universal reporting of incidental vascular calcification in routine radiological practice should be discussed and further developed.

Our data provide evidence for the established direct association between certain pulmonary diseases and CVD [16–19], as airway thickening, ground glass, consolidation, pleural effusion and lymphadenopathy were demonstrated to be associated with CVD risk. This positive relation can be explained because an important mutual cause for these imaging findings, inflammation, has a central role in the atherosclerotic process precipitating CVD events [27–30]. Consistent with our findings, markers of inflammation measurable in serum or plasma (e.g. high sensitivity C-reactive protein, interleukin 6, fibrinogen) have also been associated with CVD risk [31]. Additionally, some abnormalities reflect (subclinical) heart failure. The most common cause of bilateral pleural effusion is heart failure [27]. Bilateral effusion can be a direct marker of CVD, explaining the significant association between pleural effusion and CVD risk even after adjustment for cardiovascular imaging features.

When adjusted for cardiovascular imaging features, only ground glass, pleural effusion and lymphadenopathy were demonstrated to be independently associated with CVD event risk. This may indicate that these pulmonary disease-related CT findings exert their hazardous effect on future CVD events through other pathways than those through which cardiovascular findings affect CVD risk. However, as these abnormalities may reflect (subclinical) heart failure it could well be that they are merely a consequence of the disease. Ground glass, pleural effusion and lymphadenopathy were selected for addition to the cardiovascular CT features model as they were independently associated with CVD. Using a forward stepwise procedure resulted in identical predictor selection. Although these features were independently associated with the risk of later CVD events, their incremental value beyond cardiovascular findings was marginal. Addition of these three imaging features to the cardiovascular CT features model

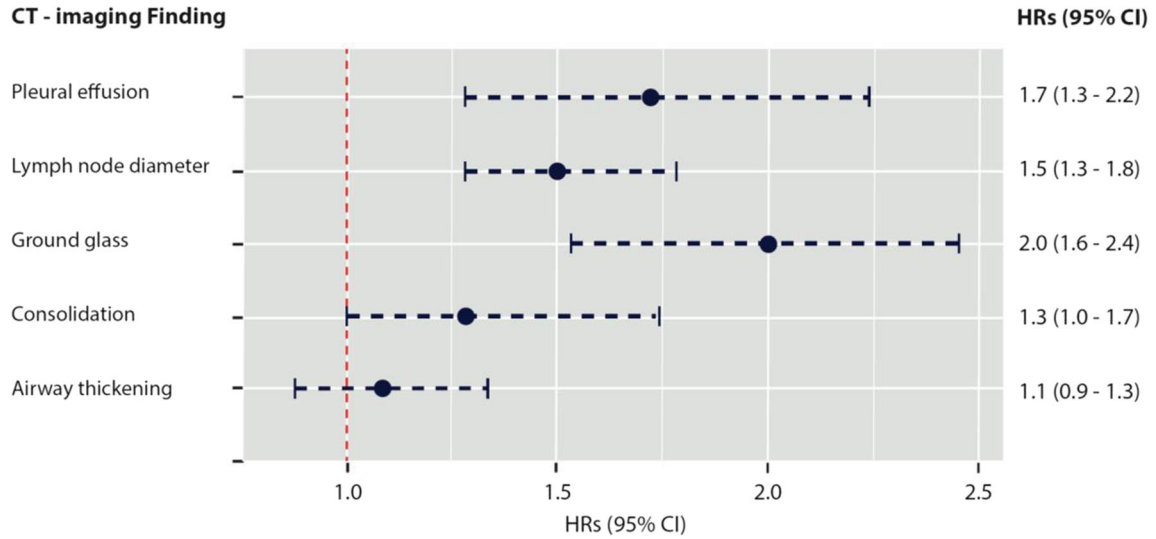

Fig. 3 Multivariable-adjusted hazard ratios (HRs) and 95 % confidence interval (95 % CI) for cardiovascular events comparing the severe versus the absent category of pleural effusion (HR 1.7 [95 % CI 1.3–2.2]), lymph node diameter (HR 1.5 [95 % CI 1.3–1.8]), airway thickening (HR 1.1 [95 % CI 0.9–1.3]), consolidation (HR 1.3 [95 % CI 1.0–1.7] and ground glass (HR 2.0 [95 % CI 1.6–2.4])

yielded an NRI in the intermediate-risk group of less than 10 %, falling below reclassification thresholds that are considered clinically relevant [32].

Limitations

One of the limitations of our study that merits consideration is that our cohort was comprised of a population of Caucasian Dutch descent. Therefore the generalizability of our findings to populations of different racial or ethnic backgrounds remains uncertain. Another issue that merits consideration is that assessment of pulmonary CT findings like consolidations, ground glass and airway thickening had a relatively low inter-reader reliability. This may have influenced the association between these findings with CVD events. Moreover, we favoured not to use expert cardiothoracic radiologists as in our practice most chest CT images are interpreted by general radiologists, and often the lungs are read by cardiac radiologists and the arteries by chest radiologists. We think that the quality of the readers will have minimally affected the results. Additionally, the CT examinations varied in slice thickness, use of contrast medium and CT machine vendors. This may have given rise to the possibility of missing subtle CT findings like small coronary artery calcification, bronchial wall thickening and ground glass opacity. However, our visual assessment of the CT findings is a real practice scenario, where visual assessment based on a variety of protocols, also compared to quantitative assessment, has been demonstrated to be relatively simple, inexpensive and independent of machine and reconstruction algorithms [33]. Lastly, in prognostic research, candidate predictors should be measured using methods easily applicable—or potentially applicable—to daily practice [34].

Table 4 Discrimination and reclassification estimates for cardiovascular events (n=1,148 events) during a median follow-up period time of 3.7 years according to the cardiovascular CT features model without and with addition of pulmonary, mediastinal and pleural chest CT findings

	Cardiovascular CT features model[c]	Cardiopulmonary CT features model[d]
C-statistic (95 % CI)[a]	0.72 (0.71–0.74)	0.74 (0.72–0.75)
Net Reclassification Index (NRI) (95 % CI)[b]	NA	6.50 (4.44–8.55)

[a] C-statistic is corrected for over optimism by using 150 bootstrap repetitions

[b] Percentage of NRI (95 % CI) for the cardiovascular CT features model versus the cardiopulmonary CT features model, using 5-year predicted cardiovascular risks and risk categories of <5 %, 5–10 % and >10 %

[c] Cardiovascular CT features model included the following variables: age, gender, CT indication, left anterior descending coronary artery calcification, mitral valve calcification, descending aortic calcification and the cardiac diameter

[d] Cardiopulmonary CT features model included the following variables: age, gender, CT indication, left anterior descending coronary artery calcification, mitral valve calcification, descending aortic calcification and the cardiac diameter plus ground glass, pleural effusion and lymph node diameter

Conclusion

Ground glass, pleural effusion and lymphadenopathy on routine clinical CT examinations were independent predictors of future CVD events. However, addition of these imaging features to a risk model based on cardiovascular findings only marginally improves 5-year CVD event risk prediction in a Caucasian Dutch population. Pulmonary, mediastinal and pleural features have limited predictive value in the identification of subjects at high risk of CVD events beyond cardiovascular findings on diagnostic chest CTs.

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