Computed tomography on lung cancer screening is useful for adjuvant comorbidity diagnosis in developing countries

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Abstract

Purpose The aim of this study was to analyse and quantify the prevalence of six comorbidities from lung cancer screening (LCS) on computed tomography (CT) scans of patients from developing countries.

Methods For this retrospective study, low-dose CT scans (n=775) were examined from patients who underwent LCS in a tertiary hospital between 2016 and 2020. An age- and sex-matched control group was obtained for comparison (n=370). Using the software, coronary artery calcification (CAC), the skeletal muscle area, interstitial lung abnormalities, emphysema, osteoporosis and hepatic steatosis were accessed. Clinical characteristics of each participant were identified. A t-test and Chi-squared test were used to examine differences between these values. Interclass correlation coefficients (ICCs) and interobserver agreement (assessed by calculating kappa coefficients) were calculated to assess the correlation of measures interpreted by two observers. p-values <0.05 were considered significant.

Results One or more comorbidities were identified in 86.6% of the patients and in 40% of the controls. The most prevalent comorbidity was osteoporosis, present in 44.2% of patients and in 24.8% of controls. New diagnoses of cardiovascular disease, emphysema and osteoporosis were made in 25%, 7% and 46% of cases, respectively. The kappa coefficient for CAC was 0.906 (p<0.001). ICCs for measures of liver, spleen and bone density were 0.88, 0.93 and 0.96, respectively (p<0.001).

Conclusions CT data acquired during LCS led to the identification of previously undiagnosed comorbidities. The LCS is useful to facilitate comorbidity diagnosis in developing countries, providing opportunities for its prevention and treatment.

Introduction

Lung cancer is the second most prevalent cancer and the leading cause of cancer death in 2020, with 2.2 million new cancer cases and 1.8 million deaths [1]. It has been one of the main causes of cancer deaths worldwide for >30 years, with a 5-year survival rate of 20.5% in the period 2010–2016 and 21.7% in the period 2011–2017 [2, 3]. This low survival rate is due in part to late diagnosis (only 16% of cases are diagnosed in the initial stage) and the complexity of its symptoms; it can appear late with smoking-related comorbidities [3, 4].

Lung cancer incidence and mortality rates are higher in developed countries than in developing countries, and this pattern may well change as the tobacco epidemic evolves owing to most smokers being from developing countries [5]. In Brazil, the number of lung cancer cases is increasing continuously due to increasing smoking rates, and the government has implemented a campaign for tobacco control to reduce the prevalence of smokers [6].

The National Lung Screening Trial (NLST) conducted in 2002–2009 demonstrated that low-dose computed tomography (CT) could reduce lung cancer mortality in current and ex-smokers by identifying suspected cases of lung cancer at an early stage [4]. Screening with low-dose CT reduced mortality from lung cancer by 20.0% compared with chest radiograph-based screening [4]. Nevertheless, the problematic nature of smoking-related comorbidities has been described in reports on lung cancer screening (LCS) [4]. Cigarette smoking affects multiple organ systems, and most trial participants are unaware of the comorbidities they have, which can result in death during the study period [4].

Chronic diseases related to smoking identified in previous LCS studies, and commonly found on chest CT, include osteoporosis and pulmonary (emphysema and interstitial lung abnormalities (ILAs)) and cardiovascular disease [7–9]. ILAs are non-dependent abnormalities identified incidentally in patients without clinical suspicion of interstitial lung disease (ILD), when ILD may be compatible with these abnormalities [10, 11]. Furthermore, there are subcategories of ILAs including: non-subpleural, subpleural non-fibrotic and subpleural fibrotic [9, 11].

Other smoking-related diseases also identified in LCS studies and associated with lung cancer such as hepatic steatosis and sarcopenia were also considered in this study [12, 13]. Sarcopenia is characterised by the loss of muscle mass and function and affects mainly elderly adults, such as those participating in our study [14–16]. The identification of these conditions in LCS participants is important, as it enables their treatment and contributes to patient prognoses [4, 7, 17].

Chronic diseases are increasing in global prevalence and seriously threaten developing nations' ability to improve the health of their populations. Although often associated with developed nations, the presence of chronic disease has become the dominant health burden in many developing countries. The rise of lifestyle-related chronic disease in poor countries is the result of a complex constellation of social, economic and behavioural factors [18].

This study aimed to analyse and quantify the prevalence of six smoking-related comorbidities (osteoporosis, sarcopenia, emphysema, ILAs, coronary artery calcification (CAC) and hepatic steatosis) in a cohort of patients undergoing LCS *via* thoracic CT assessment in developing countries.

Patients and methods

For this retrospective study, low-dose CT scans from patients who underwent LCS in a tertiary hospital between 2016 and 2020 were examined. Subjects aged >55 and <80 years with a smoking history of at least 30 pack-years (packs per day×years smoked) or who had quit smoking within the previous 15 years were included. Some patients were excluded owing to CT motion artefacts (19) and others owing to the unavailability of images (10); the final cohort consisted of 775 patients (602 men) with a mean±$_{SD}$ age of 64±6.8 years. All patients included were smokers or ex-smokers (median 36.7 pack-years (range 30–79)). Patients' medical records were reviewed to identify any previous diagnoses of the comorbidities examined in this study. Control patients (n=370; 288 men with a mean age of 62±6.5 years) matched by age and sex having a low-dose CT scan for pulmonary nodule controls were reviewed for comparison. These patients were selected randomly from the same time period as the screening lung cancer group. The control participants were from a cohort of a programme in a tertiary hospital staging extrathoracic skin cancer. All controls included were also smokers or ex-smokers (median 23.5 pack-years (range 2–70)). Reviewers were blinded because of the nature of the respective scans (CT). This study was approved by the institution's research ethics committee (58815316.9.0000.5335). Informed consent was not required. CT settings are described in supplementary table S1.

Image interpretation

A protocol (table 1) was developed for the quantitative evaluation of the CT images, which included assessment for CAC, ILAs and emphysema, determination of the skeletal muscle area (SMA) and examination of vertebral bone density, and liver fat analysis using Chest Imaging Platform software (Applied Chest Imaging Laboratory/Brigham and Women's Hospital, Boston, MA, USA). Two radiologists with >10 years of chest radiology experience and training in thoracic anatomy and the features of the software used performed the CAC, ILAs, emphysema, vertebral bone density and liver fat analyses.

TABLE 1 The computed tomography (CT) protocol evaluation parameters for the six comorbidities described

Comorbidity evaluation	Parameter
CAC (visual calcium method)[#,¶]	Score 0: no CAC Score 1: mild CAC (<1-cm calcification plaque) Score 2: moderate CAC (1–2-cm calcification plaque) Score 3: heavy CAC (>2-cm calcification plaque)
Emphysema (LAA% <–950 HU)[+]	>2.5%
ILAs (HAAs %; –600 to –250 HU)[§]	>9.77%
Hepatic steatosis (≠ in liver and spleen attenuation)[f,##]	>10 HU
Sarcopenia (SMA – L3 level)[¶¶]	<55 cm^2/m^2 (men) <39 cm^2/m^2 (women)
Osteoporosis (bone density – HU)[++]	<100 HU

CAC: coronary artery calcification; LAA: low attenuation area; ILAs: interstitial lung abnormalities; HU: Hounsfield unit; HAA: high attenuation area; ≠: difference; SMA: skeletal muscle area. [#]: Neves *et al.*, 2017 [19]; [¶]: Chiles *et al.*, 2015 [17]; [+]: Wang *et al.*, 2013 [26]; [§]: Lederer *et al.*, 2009 [27]; [f]: Davidson *et al.*, 2006 [28]; [##]: Chen *et al.*, 2017 [12]; [¶¶]: Derstine *et al.*, 2018 [16]; [++]: Marinova *et al.*, 2015 [20].

CT assessment of comorbidities

CAC

CAC evaluation was performed using the visual calcium method, based on previous studies [17, 19]. The radiologists ranked the presence of calcium in the coronary artery (mild, moderate and severe) on the CT images. They also performed segmented vessel-specific scoring using an ordinal scale of 0–3: 0=no CAC; 1=mild CAC (<1-cm calcification plaque); 2=moderate CAC (1–2-cm calcification plaque); 3=heavy CAC (>2-cm calcification plaque) (figure 1).

Vertebral bone density

To evaluate osteoporosis, quantitative bone density analysis was performed using the previously described software (3DSlicer) [20]. Using a region of interest (ROI) tool (areas of 1.5–3 cm^2), bone density in the T12 vertebral region was measured on the CT images in Hounsfield units (HU) while avoiding cortical bone (figure 2). Densities <100 HU were considered to indicate osteoporosis, according to a previous study [20].

SMA

Sarcopenia was evaluated in the lumbar region (L3) using the reference values of the European Working Group on Sarcopenia in Older People [15] in the previously described software (3DSlicer). The SMA and the mean radiation attenuation of skeletal muscle were determined using previously described methods [16, 21, 22]. The HU range used for skeletal muscle was −29 to 150 HU. The L3 muscle index (centimetres squared/metres squared) was defined as the cross-sectional area of muscle at the L3 level, normalised for stature as is conventional for body mass index calculation. L3 muscle indices <55 cm^2/m^2 for men and <39 cm^2/m^2 for women were considered to indicate sarcopenia (figure 3) [23].

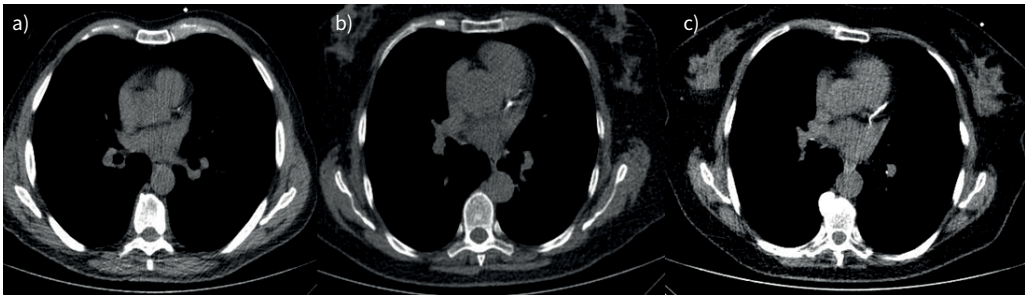

FIGURE 1 Examples of coronary artery calcification (CAC) analysis for the diagnosis of coronary artery disease from axial computed tomography images acquired without contrast. a) Mild CAC (score=1) in a woman aged 65 years. b) Moderate CAC (score=2) in a woman aged 55 years. c) Heavy CAC (score=3) in a woman aged 60 years.

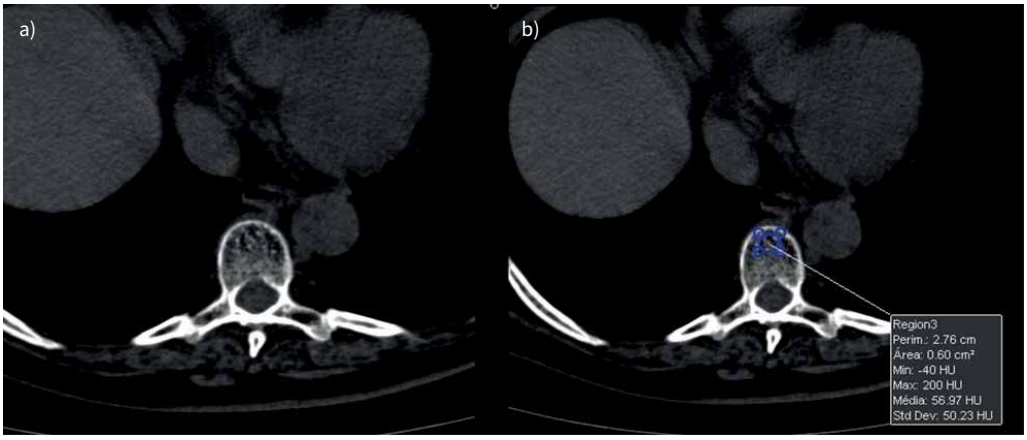

FIGURE 2 A 75-year-old woman with osteoporosis. a) Bone density was evaluated in the T12 region. b) A region of interest (area, 1.5–3 cm^2) was placed while avoiding cortical bone for the determination of bone density in Hounsfield units.

Pulmonary densitometry

Emphysema and ILAs were evaluated based on the quantification of pulmonary density and volume (figure 4) using the described software (3DSlicer), with linear attenuation values ranging from –1000 to 3095 HU [24]. The emphysema index (EI) was calculated as the percentage of low attenuation areas (LAA <–950 HU) in the lung parenchyma [24–26]. EI values >2.5% were taken to reflect emphysema [26]. High attenuation areas (HAAs; –600 to −250 HU) were also identified, and ILAs were defined as HAA% >9.77% [27]. The total pulmonary volume (in millilitres) was also calculated.

Liver fat analysis

The diagnosis of hepatic steatosis was based on the analysis of liver fat (figure 5). Liver and spleen average attenuation was assessed using the ROI tools of the described software (3DSlicer) [12, 28]. ROIs of the same size (areas of 1.5–3 cm^2) were placed in the left lateral, left medial, right anterior and right posterior hepatic sections and in the upper, middle and lower thirds of the spleen with the avoidance of large vessels and lesions. The difference between the mean attenuations of the two organs was then calculated for the establishment of a cutoff point for the diagnosis of hepatic steatosis (difference in attenuation >10 HU).

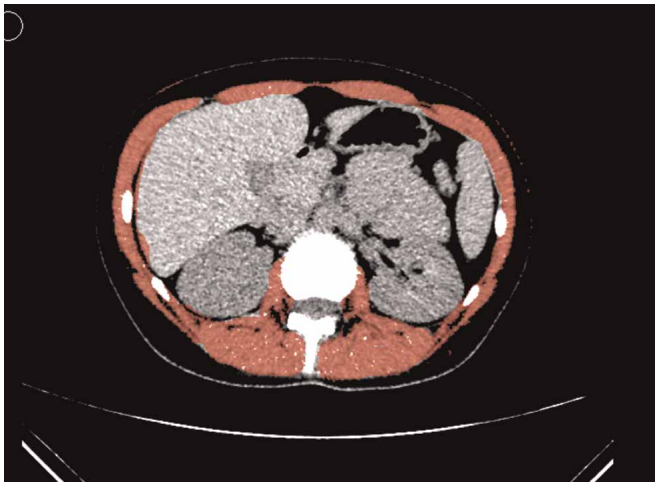

FIGURE 3 A 60-year-old man with sarcopenia. Computed tomography images extending inferiorly from L3 were evaluated automatically. After application of a predefined Hounsfield unit threshold, the boundaries were corrected manually when necessary.

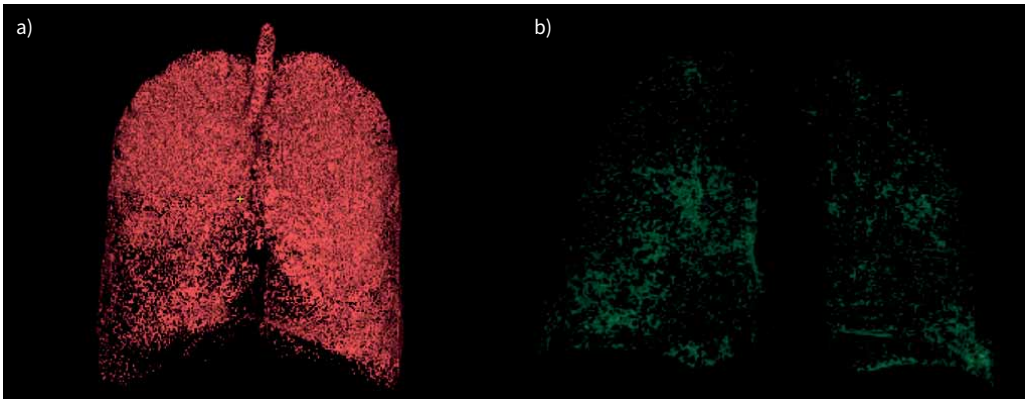

FIGURE 4 Examples of pulmonary densitometry analysis for the diagnosis of interstitial lung abnormalities (ILAs) and emphysema using reconstruction and automated detection. a) Severe emphysema in a 65-year-old man. b) Moderate ILAs in a 65-year-old man.

Statistical analysis

The statistical analyses were performed using SPSS software (ver. 2.6; SPSS Inc., Chicago, IL, USA). Continuous variables distributed normally were expressed as mean±$_{SD}$. Discrete variables were expressed as frequencies with percentages. Clinical characteristics of each participant were identified with the mean of lung densitometry values, and the t-test and Chi-squared test were used to examine differences between these values. Interobserver agreement was assessed by calculating kappa coefficients. Interclass correlation coefficients (ICCs) were calculated to assess the correlation of the reliability measures interpreted by the two observers, such as measures of liver, spleen and bone density. p-values <0.05 were considered significant.

Results

A total of 775 thoracic CT scans were analysed for the presence of CAC, emphysema, ILAs, sarcopenia, osteoporosis and hepatic steatosis. The mean or median lung densitometry values found in CT scans are given in table 2. One or more comorbidities were identified in 86.6% of the patients and in 40% of controls (table 3). Emphysema was identified in 66.3% of patients and in 8.9% of controls, osteoporosis was present in 44.2% of patients and in 24.8% of controls, CAC was identified in 41.9% of cases and in 23.7% of controls, hepatic steatosis was identified in 40.7% of cases and in 15.9% of controls, ILAs were identified in 32.2% of patients and in 12.7% of controls, and sarcopenia was identified in 9.9% of patients

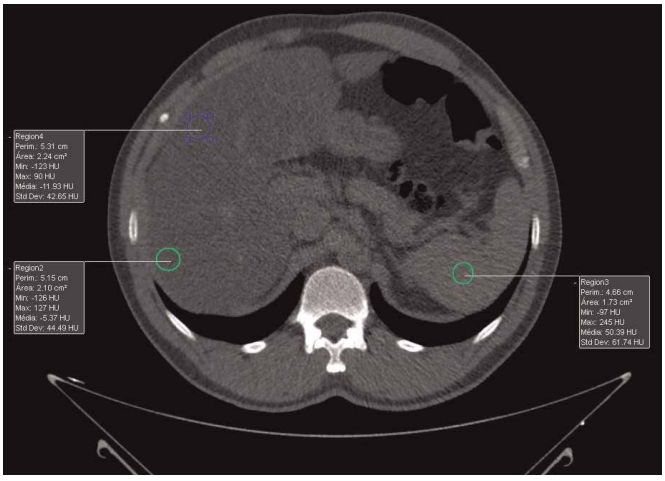

FIGURE 5 A 65-year-old man with hepatic steatosis. Attenuation of the liver (regions 2 and 4) and spleen (region 3) was assessed using region of interest tools in post-processing programs.

TABLE 2 Low-dose computed tomography (CT) findings in patients undergoing lung cancer screening (n=775)

CT characteristic	Mean±SD or median (IQR)
Lung volume mL	5945±1411
Lung volume mL, –950 to 700 HU	4570±1036
Lung volume %, –950 to 700 HU	77.5±9.2
Lung volume mL, –700 to 250 HU	555 (±466.7–659.4)
Lung volume %, –700 to 250 HU	10.5±5.2
Emphysema index	10.4 (4–16.7)
Hepatic steatosis	8.9 (3–16)
Liver density (HU)	62.6±10.1
Spleen density (HU)	53.9±6.0
Bone density (HU)	126.3±50.2
Attenuation area	
Low (950 HU)	9.2 (3.4–15.4)
High (700 HU)	8.4 (7.3–10.7)
Density HU	–839.6±36.5
Volume mL	5.8±1.4

IQR: interquartile range; HU: Hounsfield unit.

and in 3.5% of controls (table 3). New diagnoses of cardiovascular disease (comorbidities not previously diagnosed according to the medical records) were made for 25% of patients, emphysema was newly diagnosed in 7% of patients and osteoporosis was newly diagnosed in 46% of patients.

The kappa coefficient for CAC was 0.906 ($p<0.001$). ICCs for measures of liver, spleen and bone density were 0.88, 0.93 and 0.96, respectively (all $p<0.001$).

Discussion

A complex constellation of social, economic and behavioural factors is behind the rise in chronic diseases. With the luxury of hindsight, we can apply some of the lessons learned in developed countries to developing countries, but only to a limited extent. The three main risk factors for chronic diseases - overnutrition, lack of physical activity and tobacco use - are increasing generally in developing countries, just as in developed countries [18]. Poor healthcare is an important risk factor for the development of chronic diseases. As a general rule, in poor developing countries there are problems with access to healthcare and affordability of preventive care [18]. Also, primary care systems are weak and often too overloaded to respond to emerging chronic disease symptoms. Because of this, any improvement in diagnosis such as that discussed in this study could be important to improvement in health in developing countries. In our study, one or more comorbidities beyond lung cancer were identified in 86.6% of patients who underwent elective low-dose CT examinations for LCS.

TABLE 3 Comorbidities identified in patients undergoing lung cancer screening low-dose computed tomography (LDCT) (n=775) and control group (n=370)

Comorbidity	LDCT n (%)	Controls n (%)
Number of comorbidities		
0	104 (13.4)	222 (60)*
1	243 (31.4)	36 (9.7)*
2	311 (40.1)	49 (13.2)*
⩾3	117 (15.1)	63 (17)*
Interstitial lung abnormalities	247 (32.2)	47 (12.7)*
Emphysema	524 (66.3)	33 (8.9)*
Coronary artery calcification	324 (41.9)	88 (23.7)*
Hepatic steatosis	315 (40.7)	59 (15.9)*
Sarcopenia	77 (9.9)	13 (3.5)*
Osteoporosis	342 (44.2)	92 (24.8)*

LDCT: low-dose computed tomography. *: $p<0.05$.

The most prevalent comorbidity was pulmonary emphysema, identified in the majority of study participants. Lung cancer and pulmonary emphysema have the common cause of cigarette smoking, and emphysema is a risk factor for the development of lung cancer [7, 29, 30]. Emphysema is a common, usually incidental, CT finding in patients undergoing LCS [30]. Our results thus corroborate previous findings. As emphysema is a risk factor for early mortality among individuals with asymptomatic COPD, its diagnosis during LCS is very important, as it enables measures to be taken to improve patient prognoses and reduce participant death during studies [30, 31]. ILAs were also identified among the participants, and previous studies demonstrated the strong association between ILAs and mortality among smokers and individuals with COPD [27, 32]. ILAs were also reported on CT scans from previous LCS studies [8, 9].

Osteoporosis and CAC had similar prevalence rates in this study, and together were identified on >80% of the CT scans evaluated. CT enables better quantification of bone density for the diagnosis of smoking-related diseases and more effective prediction of bone fractures than does dual-energy radiograph absorptiometry (DXA) [7, 33, 34]. In this study, low bone mineral density could be identified by low-dose CT during LCS, confirming previous findings [7, 20]. Such an examination is thus a viable option for the diagnosis of osteoporosis in individuals at high risk of fracture who meet the inclusion criteria used in this study, with no need for additional imaging. CAC, the third most prevalent smoking-related comorbidity identified in this study, is a risk factor for cardiovascular disease [17]. Other than lung cancer, cardiovascular disease was the main cause of death among NLST participants [4, 17]. Some researchers have suggested that CAC quantification increases the cost–benefit ratio of LCS, as it enables measures to be taken to reduce mortality among trial participants, although no consensus on this issue has been reached in the scientific community [29, 35, 36].

Hepatic steatosis was diagnosed on 40.7% of the CT scans evaluated in this study. Low-dose CT examination performed without contrast is an objective, reproducible and noninvasive means of measuring liver fat [12, 28]. Chen *et al*. (2017) [12] demonstrated that hepatic steatosis can be identified *via* the quantification of liver and spleen density on CT scans acquired during LCS. This measure adds value to studies and contributes to the quality of life of participants in whom this comorbidity is discovered and subsequently treated. The prevalence of fatty liver described in this study corroborates with previous studies about prevalence of hepatic steatosis in LCS [12].

Another prominent comorbidity identified in this study was sarcopenia. Sarcopenia has a high impact on public health because it is associated with many comorbidities, such as osteoporosis [37]. One cohort demonstrated sarcopenia as a high risk factor for lung cancer recurrence, and also the tumours of patients with sarcopenia have higher malignant potential [13]. Imaging evaluations such as CT are considered to be the gold standard for its diagnosis, and they reduce the need for another test, but other modalities, such as DXA, are often preferred owing to their lower costs [37]. The present study demonstrates that LCS can be used to identify sarcopenia. This disease is associated with a greater risk of hospitalisation and may be responsible for unfavourable outcomes (*i.e.*, reduced quality of life and mortality) in patients with cancer who have undergone vascular surgery [38].

Our study has limitations. First, our patient controls have a diagnosis of cancer and have less exposure to smoking than our patients. Although we demonstrated CT scans can be used for osteoporosis screening without additional imaging and radiation exposure, the accuracy of this method depends on clinical and population screening objectives, and more cohorts are needed to evaluate the sensitivity and specificity of diagnostic performance measurements [20, 39]. Considering this is a retrospective study, we could not change the patient management in the present study, although we demonstrated the high LCS potential of identifying smoking-related comorbidities, using CT scans, to provide an opportunity for treatment for the participants and increase the chances of a favourable outcome. This finding is important for future studies in this area.

Conclusion

This study showed that smoking-related comorbidities (CAC, emphysema, ILAs, sarcopenia, osteoporosis and hepatic steatosis) are prevalent in patients undergoing low-dose CT examination for LCS in developing countries. These findings demonstrate the importance of integrated CT assessment as part of LCS, as the identification of such comorbidities provides the opportunity to address them, increasing the chances of favourable prognoses and outcomes for the participants.

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