**UNIVERSIDADE FEDERAL DE CIÊNCIAS DA SAÚDE DE PORTO ALEGRE – UFCSPA**

**PROGRAMA DE PÓS-GRADUAÇÃO EM PATOLOGIA**

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# Tomografia Computadorizada no diagnóstico de comorbidades relacionadas ao tabagismo em estudos de rastreamento de câncer de pulmão no Brasil

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# Tomografia Computadorizada no diagnóstico de comorbidades relacionadas ao tabagismo em estudos de rastreamento de câncer de pulmão no Brasil

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Orientador: Prof. Dr. Bruno Hochhegger.

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**Resumo da Dissertação**

**Introdução:** O rastreamento de câncer de pulmão, por meio de tomografia computadorizada de tórax (TC) é essencial para o diagnóstico precoce do câncer de pulmão e de outras comorbidades relacionadas ao tabagismo. No entanto, as comorbidades não são identificadas de forma correta durante os estudos de rastreamento (pouco realizados em países em desenvolvimento). Nesse sentido, identificar essas comorbidades durante esses estudos em países em desenvolvimento é essencial. **Objetivos:** Avaliar e quantificar a prevalência de seis comorbidades relacionadas ao tabagismo (sarcopenia, calcificação da artéria coronária (CAC), enfisema pulmonar, anormalidade intersticial e esteatose hepática). **Material e Métodos:** Nesse estudo retrospectivo, foram avaliadas TC de baixa dose (n=775) de pacientes submetidos ao rastreamento de câncer de pulmão em um hospital terciário entre os anos de 2016 e 2020. Um grupo controle pareado por idade e sexo foi obtido para comparação (n=370). Foram analisados de forma quantitativa através de um software, a presença das seis comorbidades. O teste t e o teste Qui-quadrado foram usados para avaliar as diferenças entre esses valores. Coeficientes de correlação interclasse (ICCs) e concordância do inter-observador também foram calculados. p <0,05 foram considerados significativos. **Resultados:** Uma ou mais comorbidades foram identificadas em 86,6% dos pacientes e em 40% dos controles. A osteoporose esteve presente em 44,2% dos pacientes e em 24,8% dos controles. Novos diagnósticos de doenças cardiovasculares, enfisema e osteoporose foram realizados. O coeficiente kappa para calcificação da artéria coronária foi de 0,906 (p<0,001). ICCs para medidas de fígado, baço e densidade óssea foram 0,88, 0,93 e 0,96, respectivamente (p<0,001). **Conclusão:** Os dados adquiridos

durante o estudo de rastreamento de câncer de pulmão utilizando a TC de baixa dose, identificaram as seis comorbidades tabaco-relacionadas. Nesse sentido, a TC em estudos de rastreamento, facilita o diagnóstico de comorbidades em países em desenvolvimento, fornecendo oportunidades para sua prevenção e tratamento.

**Palavras-chave:** Rastreamento, câncer de pulmão, comorbidades, tabagismo, tomografia computadorizada.

## Abstract

**Introduction:** Lung cancer screening using chest computed tomography (CT) is essential for the early diagnosis of lung cancer and other smoking-related comorbidities. However, comorbidities are not correctly identified during screening studies, which are rarely performed in developing countries. Therefore, identifying these comorbidities during these studies in developing countries is necessary. **Objectives:** To assess and quantify the prevalence of six smoking- related comorbidities (sarcopenia, coronary artery calcification (CAC), pulmonary emphysema, interstitial abnormalities and hepatic steatosis). **Material and Methods:** In this retrospective study, low-dose CT (n=775) of patients undergoing lung cancer screening in a tertiary hospital between the years 2016 and 2020, were evaluated. A control group matched by age and sex were obtained for comparison (n=370). The presence of the six comorbidities were analyzed quantitatively through a software. The t-test and the chi-square test were used to assess the differences between these values. Interclass correlation coefficients (ICCs) and interobserver agreement were calculated. $p<0.05$ were considered significant. **Results:** One or more comorbidities were identified in 86.6% of patients and in 40% of controls. Osteoporosis was present in 44.2% of patients and in 24.8% of controls. New diagnoses of cardiovascular disease, emphysema and osteoporosis were made. The kappa coefficient for CAC was 0.906 ($p<0.001$). ICCs for liver, spleen, and bone density measurements were 0.88, 0.93, and 0.96, respectively ($p<0.001$). **Conclusion:** Data acquired during the lung cancer screening study using low-dose CT identified the six tobacco- related comorbidities. In that regard, low dose CT for screening studies facilitates

the diagnosis of comorbidities in developing countries, providing opportunities for their prevention and treatment.

**Keywords:** Screening, Lung Cancer, comorbidities, computed tomography, smoking.

**Lista de abreviaturas**

AME. Área do músculo esquelético lombar;

ARME. Atenuação média da radiação do músculo

esquelético; BRELT1. *First Brazilian Lung Cancer Screening*

*Trial*; BRELT2. *Second Brazilian Lung Cancer Screening Trial;*

CAC. Calcificação a artéria coronária;

DMO. Densitometria óssea;

DAC. Doença arterial coronariana;

DPI. Doença pulmonar intersticial;

DPOC. Doença Pulmonar Obstrutiva Crônica;

DXA. Absorpiometria de raios X de dupla energia;

EUA. Estados Unidos da América;

EWGSOP*. The European Working Group on Sarcopenia in Older People;*

HAA. *High attenuation areas*;

ICC. Coeficientes de correlação interclasse;

INCA. Instituto Nacional de Câncer

LAA. *Low attenuation areas*;

MILD*. Multicentric Italian Lung Detection*;

NLST*. National Lung Screening Trial*;

OMS. Organização Mundial da Saúde

PETab. Pesquisa Especial sobre o Tabagismo

SEA. Sudeste Asiático

TC. Tomografia computadorizada;

TCQ. Tomografia Computadorizada Quantitativa;

USPSTF. US Preventive Services Task Force;

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# 1. INTRODUÇÃO

## 1.1 Câncer de pulmão

O câncer de pulmão é o segundo câncer mais prevalente e a principal causa de mortes por câncer no mundo [1]. Em 2020, foram 2.2 milhões de novos casos e 1.8 milhões de mortes [1]. Há mais de 30 anos o câncer de pulmão está entre os mais prevalentes do mundo e, segundo dados recentes, em 2022 continuará ocupando essa posição [2,3].

Dados de 2021 demonstram que essa doença possui incidência de aproximadamente 12.4%, e taxa de mortalidade de aproximadamente 21.7% [3,4]. A alta taxa de mortalidade se deve ao prognóstico desfavorável da doença e a baixa sobrevida de 5 anos [3,4]. Entre o período de 2011-2017, a taxa de sobrevida de 5 anos alcançou 21.7% dos diagnósticos e, de 2012- 2018, 22.9% [3,4]. Em países em desenvolvimento a taxa é ainda mais baixa, variando entre 7% e 10%, segundo dados do Instituto Nacional do Câncer (INCA) de 2021 [5].

Além disso, muitos indivíduos com essa doença não demonstram sintomas em estágio iniciais, o que dificulta o diagnóstico precoce [6]. Os sintomas apresentados acabam sendo complexos e muitas vezes não são claros por estarem relacionados a outras comorbidades [6].

## 1.2 Câncer de pulmão e o tabagismo

O fator de risco mais importante para o desenvolvimento do câncer de pulmão é o tabagismo [7,8]. Estima-se que 90% dos casos acometem indivíduos tabagistas ou ex-tabagistas, e esse fator pode aumentar em até 20 vezes o risco [7,8].

Em uma metanálise desenvolvida por Khuder et al. (2001) o tabagismo foi identificado como causa do desenvolvimento dos quatro principais tipos de câncer de pulmão classificados microscopicamente[9]. São eles, adenocarcinoma, carcinoma de células escamosas, carcinoma de grandes células e carcinoma de pequenas células [7,9].

E apesar da cessação do tabagismo poder trazer benefícios para o indivíduo independente da fase da vida, sabe-se que ainda há um risco de desenvolver câncer de pulmão quando se compara com indivíduos nunca fumantes [7,8]. Fatores como o tempo de tabagismo e o tempo de abstinência, influenciam no risco [7,8].

Dados da Organização Mundial da Saúde (OMS) de 2020, demonstram que 22.3% da população mundial acima de 15 anos, é usuária de tabaco, sendo na sua maioria homens (36.7%) [10]. As mulheres correspondem a 7.8% dessa prevalência [10]. Até 2030 o tabagismo pode levar a morte de 8 milhões de usuários a cada ano, e grande parte das mortes (80%) ocorrem em países de baixa e média renda [10–15].

O número de tabagistas em países desenvolvidos tem decaído nos últimos anos e em países em desenvolvimento, esse número está aumentando [10–15]. A região do Sudeste Asiático (SEA), apresentou um aumento significativo da taxa de tabagismo desde 2000[10]. Dados de 2015 demostram que, essa região em desenvolvimento representa, aproximadamente, 30% do tabagistas no mundo [10].

É importante ressaltar que mesmo com o número de tabagistas em queda em países desenvolvidos, as mortes relacionadas ao tabaco ainda são elevadas,

principalmente pelo histórico de tabagismo nesses países [10–15]. Já em países de baixa renda, devido ao crescente número de tabagistas, as mortes por doenças relacionadas ao tabagismo tendem a aumentar nos próximos anos [10–15].O tabaco contabilizou em 2019 cerca de 8 milhões de mortes [13].

Em países considerados de baixa e média renda, o cultivo e o consumo de tabaco são altos, gerando ainda mais demanda nos sistemas de saúde, devido às diversas comorbidades tabaco-relacionadas[10–15]. Essas questões agravam a situação desses países que já possuem problemáticas em relação à saúde pública e economia [10–15].

### 1.3 Câncer de pulmão no Brasil

Considerado um país em desenvolvimento, o Brasil possui uma taxa de 12% da população de fumantes ativos acima de 18 anos, segundo dados de 2019 [5]. A partir da implementação de políticas como a Pesquisa Especial sobre o Tabagismo (PETab) em 2008, da aplicação de impostos sobre a venda de tabaco e a restrição de publicidade de marcas de cigarro, observou-se uma redução importante de indivíduos tabagistas no país [5]. Entre o período de 1989 até 2008 houve uma redução de 46%, e no período de 2013 até 2019, uma redução de 14% [5]. Apesar desses dados otimistas, ainda há uma preocupação quanto a taxa de fumantes no país, pois a prevalência e mortes por câncer de pulmão aumentou nos últimos anos [5,16].

O Brasil é o país da América Latina com maior incidência e número de mortes por câncer de pulmão (Figura 1)[17]. Em 2020, foram estimados cerca de 30 novos casos a cada 100 mil homens e 16 novos casos a cada 100 mil mulheres (Figuras 2 e 3), e mais de 35 mil mortes, números que podem ser mais altos devido à

subnotificação e ao, ainda baixo, índice de diagnóstico no país [6,16–18]. Por ser um país com alta prevalência de casos de tuberculose, esse também é um fator de risco para o câncer [16,18,19].

Figura 1: Prevalência de casos de câncer de pulmão em 2020 na América do Sul, na população acima de 15 anos, de ambos os sexos. Fonte: Globocan 2020/ Global Cancer Observatory (http://gco.iarc.fr)[17]

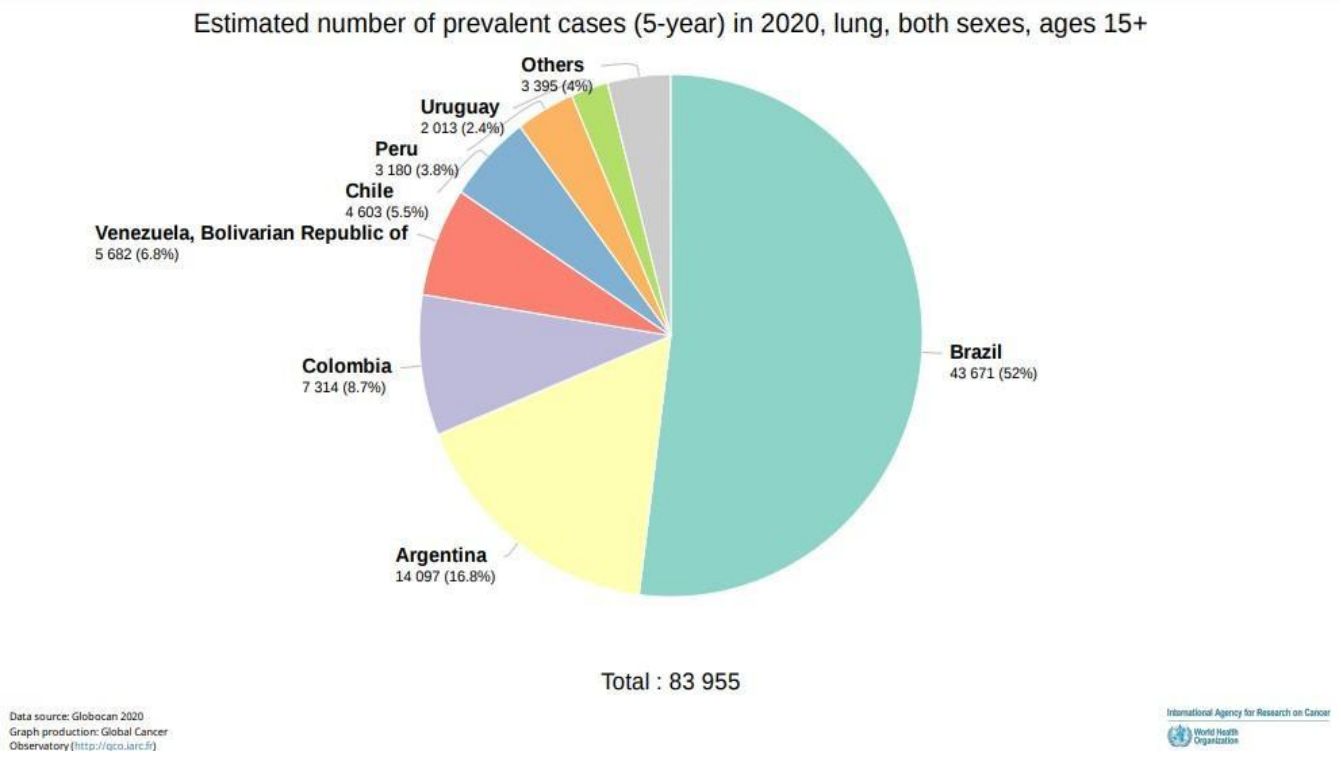


Figura 2: Incidência por 100 mil homens, estimadas para o ano de 2020, segundo Unidade da Federação (neoplasia maligna da traqueia, dos brônquios e dos pulmões). Fonte: Instituto Nacional de Câncer José Alencar Gomes da Silva. Estimativa 2020: incidência de câncer no Brasil / Instituto Nacional de Câncer José Alencar Gomes da Silva. – Rio de Janeiro : INCA, 2019 16.

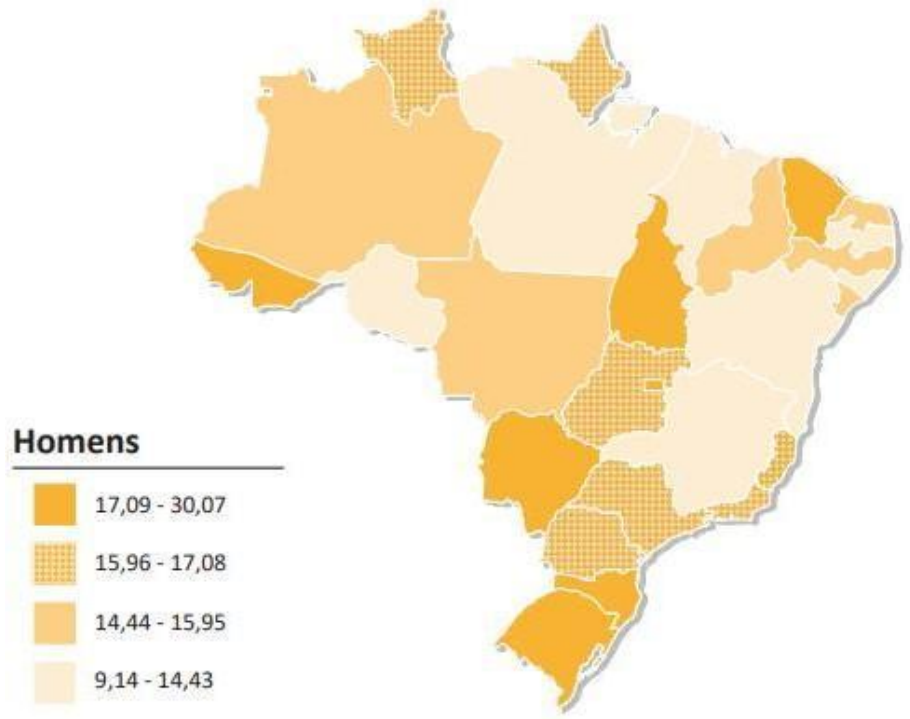
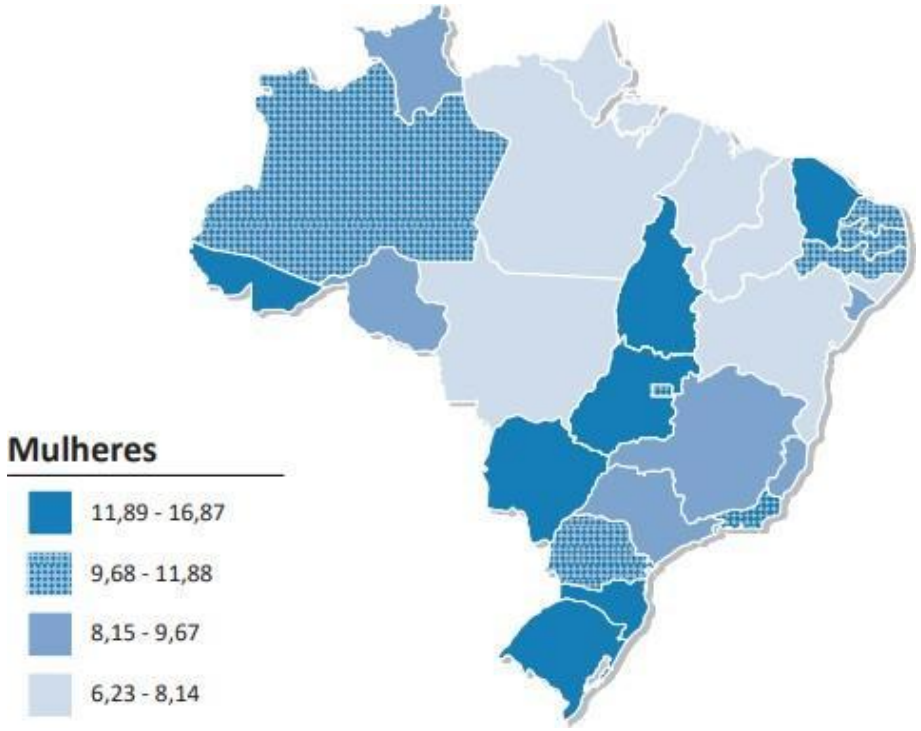


Figura 3: Incidência por 100 mil mulheres, estimadas para o ano de 2020, segundo Unidade da Federação (neoplasia maligna da traqueia, dos brônquios e dos pulmões). Fonte: Instituto Nacional de Câncer José Alencar Gomes da Silva. Estimativa 2020: incidência de câncer no Brasil / Instituto Nacional de Câncer José Alencar Gomes da Silva. – Rio de Janeiro: INCA, 2019 16.




Além disso, em países em desenvolvimento como o Brasil, o tabagismo gera custos altos ao sistema de saúde, pois o tabaco também está diretamente relacionado ao desenvolvimento de doenças pulmonares como a Doença Pulmonar Obstrutiva Crônica (DPOC) e doenças cardíacas [5,20].

Na América Latina o aumento da prevalência do tabagismo revela que se o cenário permanecer dessa forma, o câncer de pulmão será a principal causa de mortes nas próximas décadas e os sistemas públicos de saúde latino-americanos não estão preparados para essa demanda [21,22]. Nesse sentido, o diagnóstico precoce do câncer de pulmão, através de estudos de rastreamento, é muito importante para o melhor prognóstico e tratamento da doença [3]. Cerca de 20%, é a taxa de redução da mortalidade por câncer de pulmão entre indivíduos com alto risco após a participação nesses estudos [7,8,23–25].

### 1.4 Rastreamento de câncer de pulmão

O rastreamento de câncer de pulmão anual para indivíduos com alto risco é recomendado pela US Preventive Services Task Force (USPSTF), um grupo de pesquisadores dos Estados Unidos (EUA) que realiza recomendações de saúde e melhora de tratamentos para a população baseado em evidências científicas[26]. O alto risco é definido através de critérios como idade, tempo de exposição ao tabaco e há quanto tempo o indivíduo parou de fumar [26].

Os primeiros estudos de rastreamento de câncer de pulmão são datados da década de 1970 nos EUA pelo *US cancer institute,* em que a radiografia de tórax e a citologia foram utilizadas como métodos para diagnóstico precoce e redução da mortalidade [27–29]. Esses estudos não demonstraram redução significativa da mortalidade por câncer de pulmão.

Já na década de 1990, ao comparar a radiografia de tórax e TC de tórax de baixa dose, o *Early Lung Cancer Action Program* concluiu que a TC de baixa dose consegue diagnosticar nódulos pulmonares não calcificados em estágios iniciais, contribuindo para o diagnóstico precoce do câncer de pulmão [30]. Mais tarde, esse

grupo publicou outro estudo recrutando indivíduos de alto risco para o câncer entre 1993 e 2005, utilizando a TC de baixa dose para o rastreamento [31]. Neste estudo, 85% dos indivíduos foram detectados com câncer de pulmão em estágio inicial e submetidos a ressecção pulmonar, resultando em aumento da sobrevida de 92% [27,30].

Entre os anos de 2002-2009, um importante estudo multicêntrico randomizado controlado de rastreamento foi conduzido através do *National Lung Screening Trial* (NLST) [23,24]. Com o objetivo de comparar a radiografia de tórax e a TC de baixa dose para o diagnóstico precoce da doença em indivíduos tabagistas e ex- tabagistas, o estudo reuniu um número significativo de participantes, tornando-o uma referência para estudos posteriores [23]. Mais de 50 mil indivíduos foram submetidos a três rastreamentos (radiografia ou TC de baixa dose) entre agosto de 2002 e setembro de 2007 e majoritariamente, houve mais detecções positivas para câncer de pulmão a partir da TC de baixa dose em relação à radiografia [23]. Além disso, no NLST, a mortalidade por câncer de pulmão reduziu 20% no grupo submetido à TC e baixa dose, quando comparado ao grupo submetido à radiografia [24].

É possível encontrar resultados semelhantes em estudos prévios[32–35]. O estudo randomizado NELSON (2000), observou que o rastreamento através da TC de baixa dose é capaz de reduzir pelo menos 25% da mortalidade entre indivíduos de alto risco, comparado ao grupo que não realizou o estudo [24,32].

O estudo multicêntrico italiano *Multicentric Italian Lung Detection* (MILD) publicado em 2019, observou em 10 anos, uma redução do risco de mortalidade

em 20% nos indivíduos submetidos a TC de baixa dose no estudo de rastreamento [33–35].

Isso tudo devido ao rápido desenvolvimento tecnológico da TC e a redução da radiação em relação à radiografia [6,36,37]. Esse exame de imagem detecta anormalidades de forma mais sensível e acurada. No caso da TC de baixa dose, a radiação é ainda menor que a TC convencional, cerca de 25% a menos[38].

### 1.5 Rastreamento de câncer de pulmão no Brasil

O primeiro estudo de rastreamento de câncer de pulmão no Brasil, *First Brazilian Lung Cancer Screening Trial* (BRELT1), reuniu 790 indivíduos que possuíam os critérios de inclusão, definidos previamente pelo NLST (2011), entre janeiro de 2013 e junho de 2014 [18,22,27,39]. O estudo foi o primeiro realizado em uma região endêmica para tuberculose, e observou 35% de casos com rastreamento positivo, mais do que em estudos prévios[22]. No entanto, seguindo o protocolo para avaliação das lesões, poucos casos foram encaminhados para procedimentos invasivos e grande parte dos casos apenas seguiram realizando o rastreamento para controle de evolução [22].

O segundo estudo de rastreamento de câncer de pulmão no Brasil (BRELT2) avaliou 3.470 mil voluntários de seis grandes centros no país entre dezembro de 2013 até fevereiro de 2020, seguindo os mesmos critérios do estudo anterior [22,39]. Dos indivíduos avaliados nesse estudo, 6.3% possuíam achados suspeitos para câncer de pulmão, sendo que 3.1% foram submetidos à exames minimamente invasivos e 2.1% receberam o diagnóstico de câncer de pulmão [39]. Esses achados foram considerados semelhantes em relação ao estudo prévio [22].

Apesar de se mostrar muito importante, como demonstraram os estudos citados anteriormente, o rastreamento de câncer de pulmão no Brasil ainda está em debate assim como em outros países em desenvolvimento [18]. Fatores como custo-efetividade e viabilidade, são colocados em discussão para análise [18,19,27]. Em um país com alta incidência de casos de tuberculose (31,6 /100 mil habitantes em 2020, segundo o Ministério da Saúde), e de outras doenças crônicas pulmonares, que já acarretam gastos para o sistema público de saúde, o rastreamento de câncer de pulmão fica em segundo plano [18,22,27].

Outro fator a ser considerado é o número de tomógrafos no país disponíveis no sistema público de saúde, considerando que o sistema privado de saúde no Brasil possui a quantidade de aparelhos equivalente a seis vezes mais que o sistema público [39]. No entanto, autores desses estudos prévios acreditam que a partir dos resultados satisfatórios já obtidos, é possível que ocorra um estímulo para a organização e criação de programas de rastreamento de câncer de pulmão no Brasil e em outros países da América Latina [22,39].

### 1.6 Rastreamento de câncer de pulmão e comorbidades tabaco-relacionadas

Além do rastreamento de câncer de pulmão ser essencial para o diagnóstico precoce e melhora do prognóstico da doença, a partir dele é possível identificar outras comorbidades relacionadas ao tabagismo as quais possuem alta morbidade e mortalidade [40].

Durante os estudos de rastreamento, participantes acabam sendo diagnosticados com comorbidades relacionadas ao tabagismo que até então eram desconhecidas por eles. Essas doenças muitas vezes são diagnosticadas

de forma tardia ou apenas após o óbito desses indivíduos durante os estudos[40–44].

A TC de tórax de baixa dose, utilizada nos estudos de rastreamento, é capaz de fornecer achados e informações importantes para o diagnóstico de doenças relacionadas ao tabagismo [40,45]. Doença arterial coronariana (DAC), osteoporose, e doenças pulmonares, são exemplos de comorbidades que podem ser identificadas e quantificadas através de achados específicos que a TC proporciona [42,46–48]. É possível também encontrar achados sugestivos de esteatose hepática e sarcopenia através das imagens tomográficas de tórax [49–52].

N. Sverzellati et al (2011), analisaram a presença de achados sugestivos de doença pulmonar intersticial (DPI) no estudo MILD (n=692), e observaram esse padrão em 9.5% dos indivíduos, concluindo que não é incomum diagnóstico dessa doença pulmonar em estudos de rastreamento [47] (Tabela 1).

Posteriormente, N. Sverzellati et al (2012) no mesmo ensaio multicêntrico Italiano, publicaram outro estudo que observou a relação entre a prevalência de enfisema, CAC e a associação desses fatores com a mortalidade [46]. O estudo demonstrou que a avaliação da CAC através da TC de tórax auxilia na predição do risco de doença cardiovascular e, consequentemente, melhora o prognóstico do indivíduo [46]. Além disso, apesar da relação entre enfisema e mortalidade não ter sido significativa, sabe-se que a extensão de enfisema avaliada através da TC de tórax, é preditiva de mortalidade para doenças respiratórias e cardiovasculares [46,53] (Tabela 1).

Mets et al (2011), avaliaram quando os estudos de rastreamento de câncer de pulmão poderiam ser utilizados para identificar pacientes com COPD[42]. Os participantes (n=1140) do estudo NELSON foram avaliados através da espirometria e TC de tórax em um estudo de rastreamento em andamento[42]. Ao final do estudo foi observado que, a TC de tórax demonstrou uma sensibilidade de 63% e especificidade de 88% para diagnóstico de DPOC em relação à espirometria [42] (Tabela 1).

Regan EA et al (2019), realizaram um grande estudo com o objetivo de identificar a presença de três comorbidades relacionadas ao tabagismo, são elas DAC, osteoporose e enfisema pulmonar [54]. Os participantes fazem parte do COPDGene®, um estudo epidemiológico de coorte longitudinal com indivíduos já diagnosticados com DPOC [41,55]. Desses, foram selecionados pacientes que preenchiam os critérios para o estudo de rastreamento de câncer de pulmão [54]. Nesse estudo, 4.078 mil participantes tiveram suas tomografias avaliadas para achados relacionados às comorbidades selecionadas, são elas enfisema pulmonar, CAC e osteoporose [54]. Os resultados demonstraram que em 76% dos participantes foi identificada a presença de pelo menos umas das comorbidades: 56% foram diagnosticados com osteoporose, 45% com enfisema e 44% com DAC [54]. Além disso, outro dado importante foram os novos diagnósticos. Dos participantes diagnosticados com osteoporose e DAC, 45% e 25%, respectivamente, não tinham conhecimento do mesmo até o momento do estudo [54] (Tabela 1).

Tabela 1. Principais estudos que identificaram comorbidades relacionadas ao tabagismo em estudos de rastreamento de câncer de pulmão por TC de baixa-dose.

| Estudos | Estudo de Rastreamento de câncer de pulmão | Objetivos | Comorbidades avaliadas | Resultados |
|---|---|---|---|---|
| N. Sverzellati et al. (2011)[47] | Ensaio multicêntrico italiano de rastreamento de câncer de pulmão (n=692), MILD | Analisar presença achados sugestivos de DPI no MILD | DPI | Prevalência de DPI nos participantes de 9.5%. |
| N. Sverzellati et al. (2012)[46] | Ensaio multicêntrico italiano de rastreamento de câncer de pulmão (n=1.159), MILD. | Observar a relação entre a prevalência de enfisema, CAC e a associação desses fatores com a mortalidade | Enfisema; CAC | Avaliação da CAC através da TC de tórax auxilia na predição do risco de doença cardiovascular; O enfisema é preditivo de mortalidade para doenças |

| | | | | |
|---|---|---|---|---|
| | | | | respiratórias e cardiovasculares |
| Mets et al. (2011)[42] | Dutch and Belgian Lung Cancer Screening Trial (NELSON) | Avaliar a importância dos estudos de rastreamento de câncer de pulmão para a identificação de pacientes com DPOC. (n=1140) | DPOC | TC de tórax demonstrou uma sensibilidade de 63% e especificidade de 88% para diagnóstico de DPOC |
| Regan EA et al. (2019)[54] | COPD Genetic Epidemiology study (COPDGene®) | (n=4078) | CAC, enfisema e osteoporose | Em 76% dos participantes uma ou mais comorbidades foram |

| | |
|---|---|
| | diagnosticadas A prevalência de osteoporose, enfisema e CAC foram de56%, 45% e 44 %, respectivamente. |

CAC. Calcificação da artéria coronária; DPI. Doença pulmonar intersticial; DPOC. Doença pulmonar obstrutiva crônica; MILD. *Multicentric Italian Lung Detection;* COPDGene®. COPD Genetic Epidemiology study; NELSON. Dutch and Belgian Lung Cancer Screening Trial;

A identificação dessas comorbidades, permite que o paciente tenha um tratamento adequado e, agrega valor aos estudos de rastreamento.

## 1.7 Comorbidades identificadas em estudos de rastreamento de câncer de pulmão

### *1.7.1 Doenças pulmonares*

A TC de tórax para diagnóstico de outras doenças pulmonares já é realidade e considerada padrão-ouro [6,36,37]. O diagnóstico por imagem avançou ainda mais com o desenvolvimento de softwares com o objetivo de simplificar as análises da Tomografia Computadorizada Quantitativa (TCQ) [36]. A TCQ é utilizada para quantificação de enfisema e de anormalidade intersticial [36,44,56–58].

A espirometria também é utilizada para avaliar os sintomas clínicos do paciente para o diagnóstico de doenças pulmonares, como a DPOC [59–61]. Porém, em pacientes assintomáticos e sem fatores de risco, esse exame não é indicado [62,63]. Nesse sentido, recomenda-se a realização de TC quando há divergência quanto ao resultado do exame clínico em pacientes assintomáticos [60]. Além disso, a TC oferece dados quantitativos para o diagnóstico de DPOC, característicos de enfisema pulmonar e outras doenças das vias aéreas [36,64].

A quantificação é realizada a partir das análises de densidade e volume do parênquima, dessa forma é possível avaliar a área que está afetada em relação as áreas semelhantes à normalidade [65]. A grande vantagem da TCQ, é a avaliação mais precisa e não invasiva do pulmão, além de poder diagnosticar doenças pulmonares de forma precoce antes do paciente manifestar sintomas [45,65].

O diagnóstico de enfisema é realizado a partir do cálculo de áreas com baixa densidade no parênquima pulmonar (*low attenuation áreas,* em inglês- LAA) e a densidade é definida por unidades de Hounsfield (escala que mede o coeficiente de atenuação de um feixe de raios-x que atravessam o corpo) [66]. A escala utilizada para identificar áreas semelhantes à enfisema (LAA -1024 -950 UH) foi definida a partir de estudos anteriores baseados na população saudável de não tabagistas e de tabagistas, comparando com achados patológicos relacionados à doença [67–69]. A área semelhante a enfisema é a percentagem de voxel dentro do campo pulmonar que está abaixo de -950 UH [67–69]. O valor de referência para diagnóstico de enfisema é uma percentagem maior que 6% [67,68].

Assim como enfisema, as anormalidades intersticiais, que são anormalidades não dependentes identificadas incidentalmente em pacientes sem a suspeita de DPI, também são identificadas através de uma escala que avalia áreas de alta densidade ou atenuação (HAA-*high attenuation areas*) [40,57,58,70]. A escala utilizada para identificar essas áreas (HAA -700 -250 UH) também foi definida a partir de estudos anteriores [40,57,58,70].

### *1.7.2 Doença arterial coronariana (DAC)*

Segundo a Organização Mundial da Saúde OMS (2018), as doenças cardiovasculares são a principias causas de morte do mundo, considerando que metade dessas mortes são causadas pela Doença Arterial Coronariana (DAC)[71]. A DAC é identificada através da CAC e possui relação com o tabagismo, além de ser uma das principais causas de mortalidade de indivíduos ex-fumantes que realizam programas de rastreamento LCS [41,46,72,73].

A TC de tórax oferece informações com importância diagnóstica e clínica dessa doença, sendo possível detectar e fazer projeções da CAC no paciente [46,73–76]. Portanto, alguns pesquisadores acreditam que é benéfico a utilização da TC de baixa dose como triagem para esses indivíduos [46,73–76]

O método de avaliação visual é um dos métodos de avaliação utilizados na TC para avaliar a extensão das calcificações nas coronárias e posteriormente estratificar o risco cardíaco [75]. A avaliação visual foi demonstrada em estudos prévios [46,73,75–77].

Shemesh J. et al (2010), avaliaram imagens tomográficas de participantes de um estudo de rastreamento de câncer de pulmão, utilizando o método da análise visual de CAC para preditar o risco de morte por doença cardiovascular

73.

Nesse estudo foi observado um aumento de risco cardiovascular conforme o escore de CAC identificado na imagem de TC de tórax, demonstrando que essa técnica fornece informações quantitativas do risco de morte cardiovascular em participantes de estudos de rastreamento de câncer de pulmão [73].

Em outro estudo, P.C. Jacobs et al. (2010), compararam o uso da TC de baixa dose de participantes do estudo NELSON (estudo randomizado controlado de rastreamento de câncer de pulmão) para avaliação do risco de doença cardiovascular, utilizando a análise visual da calcificação da artéria torácica (*thoracic aorta calcium* -TAC) e CAC. E a avaliação da CAC demonstrou ser um preditor mais forte de evento cardiovascular que a TAC [77].

### *1.7.3 Osteoporose*

A osteoporose pode ser identificada através da avaliação da densidade óssea em exames de TC de baixa dose, utilizadas em programas de rastreamento de câncer de pulmão [54,78–81].

É uma doença crônica relacionada ao tabagismo e caracterizada por diminuição da massa óssea, degradação do tecido ósseo e por consequência os indivíduos ficam mais suscetíveis a lesões [82]. O diagnóstico precoce é importante para prevenir prováveis fraturas, pois em casos de fraturas mais graves o risco de mortalidade também aumenta [54,78–81].

Segundo as diretrizes brasileiras para o tratamento de osteoporose (2017), o diagnóstico por imagem é recomendado como uma das formas de identificar a doença, podendo ser através de raios-x da coluna torácica e lombar e da densitometria óssea (DMO), realizada na coluna lombar e fêmur proximal [82]. No entanto, estudos recentes demostraram que também é possível identificar a

osteoporose por exame de TC, o qual diminui consideravelmente a exposição do paciente à radiação [54,78–81].

Marinova et al. (2015) avaliaram a TC de tórax e de abdome em exames de rotina. Esse estudo retrospectivo utilizou como padrão de referência o exame de absorciometria de raios X de dupla energia (DXA) e a TC de tórax [78]. Após foi realizado o pós-processamento em exames de TC para identificar a baixa densidade mineral óssea nas regiões com medidas de <100 HU (nos níveis vertebrais) [78]. Nesse sentido, a TC mostrou ser um método válido para identificar rapidamente o alto risco de desenvolvimento de osteoporose [78].

### *1.7.4 Esteatose hepática*

A esteatose hepática é causada pelo acúmulo de gordura nos hepatócitos e é o achado mais comum em tomografias de abdome superior de indivíduos assintomáticos [51,52,83]. Essa comorbidade também relacionada ao tabagismo, pode ser identificada em exames de tomografia, de forma objetiva, reprodutível e não invasiva, através da densidade hepática e esplênica [51,52,83].

O estudo realizado por Chen. x et al. (2017), mediu a atenuação do fígado e do baço em TC de baixa dose sem contraste em pacientes que realizaram rastreamento para câncer de pulmão [51]. O estudo, revelou que a TC foi capaz de identificar e fornecer informações sobre a doença, além de ser um exame de melhor custo-benefício por não expor o paciente à radiação de um exame adicional [51]. Recomenda-se que se a atenuação do fígado for < 40 HU, o paciente seja encaminhado a um especialista para melhor avaliação da doença [51].

### *1.7.5 Sarcopenia*

A sarcopenia se caracteriza pela perda e diminuição da massa muscular esquelética, perda da força e funcionalidade e está relacionada a muitos fatores como tabagismo, desnutrição, idade, doenças neurodegenerativas e fatores endócrinos [50,84].

Segundo *The European Working Group on Sarcopenia in Older People* (EWGSOP), há três critérios de diagnóstico para a sarcopenia como, a baixa massa muscular, baixa força muscular e a baixa performance física [50]. A TC e uma das técnicas mais precisas capazes de avaliar a massa muscular através das imagens geradas e programas que separam a gordura de outros tecidos moles [50].

Existem pontos de corte definidos pelo EWGSOP a partir de valores de referência de indivíduos saudáveis. Esses valores são as medidas de TC da área do músculo esquelético lombar (AME) que está relacionada ao valor da massa muscular do corpo inteiro em adultos saudáveis e, a atenuação média da radiação do músculo esquelético (ARME), relacionada a função muscular por medir o conteúdo de gordura [49,85].

Derstine et al. (2018) definiram valores de corte a partir de protocolos de TC de diferentes níveis vertebrais, tórax (T1-L1), abdômen (T10-L4) e pelve (L4-L5) [49] As medidas foram obtidas através de softwares de pós-processamento de imagem após a realização do exame [49]. E a medida de ARME foi calculada pela média dos valores de AME [49]. O estudo demonstrou que é possível avaliar aspectos de sarcopenia em TC de tórax [49].

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## 3. OBJETIVOS

GERAL:

- Avaliar e quantificar de forma retrospectiva, a prevalência de seis comorbidades tabaco-relacionadas em exames de TC de tórax elegíveis de um estudo de rastreamento de câncer de pulmão no Brasil.

ESPECÍFICOS:

- Avaliar e quantificar a prevalência de enfisema e anormalidade intersticial;
- Avaliar e quantificar a prevalência de CAC para o diagnóstico de DAC;
- Avaliar e quantificar a prevalência de esteatose hepática;
- Avaliar e quantificar a prevalência de osteoporose;
- Avaliar e quantificar a prevalência de sarcopenia.

## 4. ARTIGO CIENTÍFICO REDIGIDO EM INGLÊS

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

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**CT on Lung Cancer Screening is useful for adjuvant comorbidity diagnosis in developing countries.**


## Abstract

**Purpose:** To analyze 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) from patients who underwent LCS in a tertiary hospital between 2016 and 2020 were examined. Age and sex- matched control group was obtained for comparison (n=370). Using the software, coronary artery calcification (CAC), the skeletal muscle area (SMA), interstitial lung abnormalities (ILAs), emphysema, osteoporosis, and hepatic steatosis was accessed. Clinical characteristics of each participant were identified. *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 on 24.8% of the 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.



**Keywords:** Screening; Lung cancer; Comorbidities; Computed tomography; Developing countries.

## 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 mainly cause of cancer worldwide for more than 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 due to most smokers being from developing countries [5]. In Brazil, the number of lung cancer cases is increasing continuously due to smoking rates and the government implemented a campaign for tobacco control to decline the prevalence of smokers in the country [6].

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

Chronic diseases related to smoking identified in previous LCS studies, and commonly found in chest CT, include osteoporosis, pulmonary (emphysema and 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, non-subpleural; subpleural non-fibrotic, and subpleural fibrotic [9, 11].

Other smoking-related diseases also identified in LCS studies and associated with lung cancer, as hepatic steatosis and sarcopenia were also considered in this study [12, 13]. Sarcopenia is characterized 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 the 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 behavioral factors [18].

This study aimed to analyze and quantify the prevalence of six smoking-related comorbidities [osteoporosis, sarcopenia, emphysema, ILAs, 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 had quit smoking within the previous 15 years, were included. Patients were excluded due to CT motion artifacts (19) and others due to the unavailability of images (10), the final cohort consisted of 775 patients (602 men) with a mean age of 64 ± 6.8 years. All patient included are smokers or ex- smokers, [median 36.7 pack years (30-79)]. Patients' medical records to identify any previous diagnoses of the comorbidities examined in this study, were reviewed. Control patients [(n=370) (288 men with a mean age of 62 ± 6.5 years)] matched by age and sex having an LDCT scan for pulmonary nodule controls were reviewed for comparison. These patients were selected randomly from the same time as the screening lung cancer

group. The control participants were

from a cohort of staging extrathoracic skin cancer program in a tertiary hospital. All controls included are also smokers or ex smokers, [median 23.5 pack -years (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 were described in Supplementary Table 1 (Supplementary material).

### Image Interpretation

A protocol (Table 1) were developed for the quantitative evaluation of the CT images, which includes assessment for CAC, ILAs and emphysema, determination of the 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). Two radiologists with more than 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.

### 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 (centimeters squared/meters squared) was defined as the cross-sectional area of muscle at the L3 level, normalized 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 [23].

**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 was defined by HAA%s > 9.77%[27]. The total pulmonary volume (in milliliters) 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).

**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 means ± standard deviations. 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 density, spleen, and bone density. $p$ values < 0.05 were considered significant.

## Results

A total of 775 thoracic CT-Scans were analyzed for the presence of CAC, Emphysema, ILAs, sarcopenia, osteoporosis, and hepatic steatosis. The mean of lung densitometry values found in CT-scans were described (Table 2). One or more comorbidities were identified on 86.6% of the patients and in 40% of controls. (Table 3). Emphysema was identified in 66.3 of patients and on 8.9% of controls, osteoporosis was present on 44.2% of patients and on 24.8% of controls, CAC was identified on 41.9% and on 23.7% of controls, hepatic steatosis was identified in 40.7% of cases and on 15.9% of controls, ILAs was identified in 32.2% of patients and on 12.7% of controls, and sarcopenia was identified on 9.9% of patients and on 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 behavioral 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 health care is an important risk factor for the development of chronic diseases. In poor developing countries, lack of access and affordability of preventive care is the general rule facing people [18]. Also, primary care systems are weak and often overloaded to respond to emerging chronic disease symptoms. Because of these facts, the improvement of diagnosis in the same study could be important to health improvement 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.

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 [29–31]. 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 chronic obstructive pulmonary disease, 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, 32]. ILAs was also identified among the participants and previous studies demonstrated the strong association between ILAs and mortality among smokers and individuals with chronic obstrutive pulmonary disease (COPD) [27, 33]. ILAs was also reported on CT scans of previous LCS studies [8, 9].

Osteoporosis and CAC had similar prevalence rates in this study, and together were identified on more than 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 X-ray absorptiometry (DXA) [31, 34, 35]. In this study, low bone mineral density could be identified by low-dose CT during LCS, confirming previous findings [20, 31]. A such 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, 36, 37].

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 non-invasive 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 [38]. A cohort demonstrated sarcopenia as a high risk factor of lung cancer recurrence and also, the tumor of patients with sarcopenia has higher malignant potential [13]. Imaging evaluations such as CT are considered to be the gold standards for its diagnosis, and they reduce the need for another testing, but other modalities, such as DXA, are often preferred

due to their lower costs [38]. The present study demonstrates that LCS can be used to identify sarcopenia. This disease is associated with a greater risk of hospitalization and may be responsible for unfavorable outcomes (i.e., reduced quality of life and mortality) in patients with cancer who have undergone vascular surgery [39].

Our study has limitations. First, our patient controls have a diagnosis of cancer and have less exposure to smoking than our patients. Besides 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, 40]. Considering this is a retrospective study, we couldn´t change the patient management in this 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 favorable 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 a favorable prognoses and outcomes for the participants.

## Acknowledgments

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**Table 1**

**The CT Protocol evaluation parameters to the six comorbidities**

| described Comorbidity evaluation | Parameter |
|---|---|
| CAC (visual calcium method)[a, b] | Score 0: No CAC<br>Score 1: mild CAC (<1 cm calcification plaque)<br>Score 2: moderate CAC (1–2-cm calcification plaque)<br>Score 3: heavy CAC (>2 cm calcification plaque) |
| Emphysema (LAA% <–950 HU)[c] | > 2.5% |
| ILAs (HAAs %; –600 to -250 HU)[d] | > 9.77% |
| Hepatic steatosis (≠ in liver and spleen attenuation)[e,f] | > 10 HU |
| Sarcopenia (SMA- L3 level)[g] | < 55 $cm^2/m^2$ (men)<br><39 $cm^2/m^2$ (women) |
| Osteoporosis (bone density- HU)[h] | < 100 HU |

Note. CAC- Coronary Artery Calcification; ILAs- interstitial lung abnormalities; HU- Hounsfield Unit; SMA- Skeletal Muscle Area; LAA- Low Attenuation Area; HAA- High Attenuation Area; ≠- difference. [a]Neves et al., 2017. [b]Chiles et al., 2015. [c]Wang et al., 2013. [d]Lederer et al., 2009. [e]Davidson et al., 2006. [f]Chen et al., 2017. [g]Derstine et al., 2018. [h]Marionova et al., 2015.

**Table 2**

**Low-dose CT findings in patients undergoing lung cancer screening (*n* = 775)**

| CT characteristic | Mean ± SD or median (II) |
|---|---|
| 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 |

Note. CT, computed tomography; SD, standard deviation; II, interquartile interval; HU, Hounsfield unit.

**Table 3**

**Comorbidities identified in patients undergoing lung cancer screening LDCT (*n* = 775) and control group Controls [(n=370) (p< 0.05)*]**

| **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)* |

Note. LDCT. Low dose computed tomography.

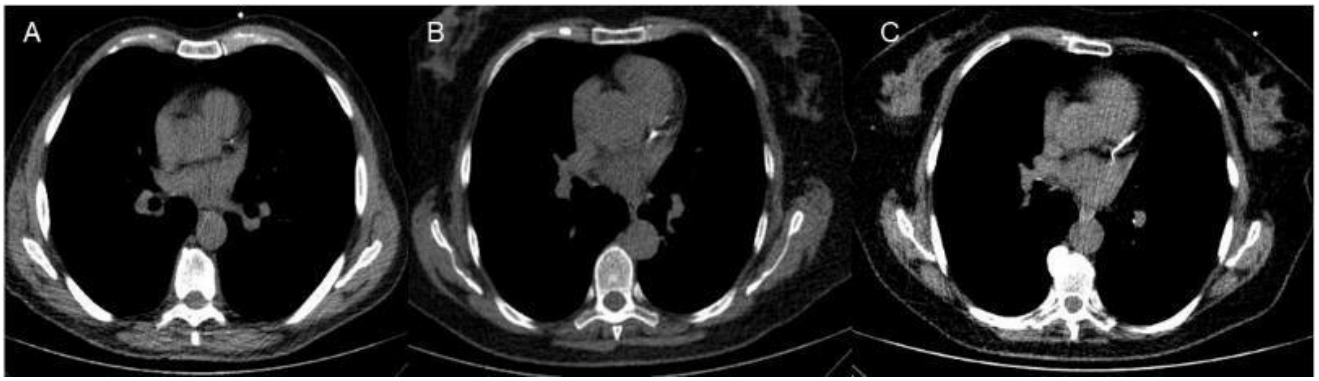


Fig. 1. Examples of CAC analysis for the diagnosis of coronary artery disease from axial CT images acquired without contrast. A, Mild CAC (score = 1) in a woman aged 65 years. B, Moderate CAC (score = 2) in a woman aged 55 years. C, Heavy CAC (score = 3) in a woman aged 60 years. CT, computed tomography; CAC, coronary artery calcification.

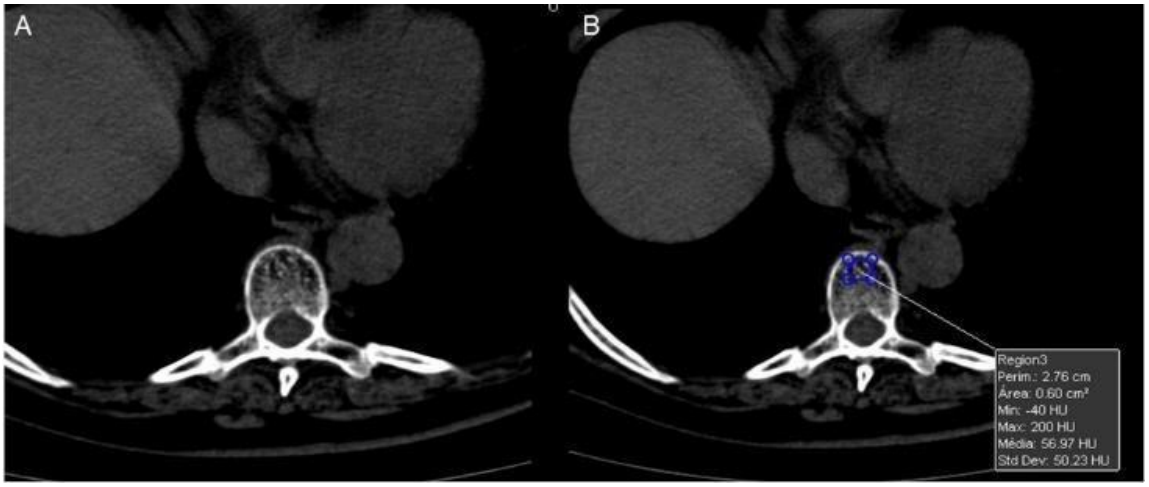


Fig. 2. 75-year-old woman with osteoporosis. A, Bone density was evaluated in the T12 region. B, A region of interest (area, 1.5–3 $cm^2$) was placed while avoiding cortical bone for the determination of bone density in Hounsfield units. CT, computed tomography.

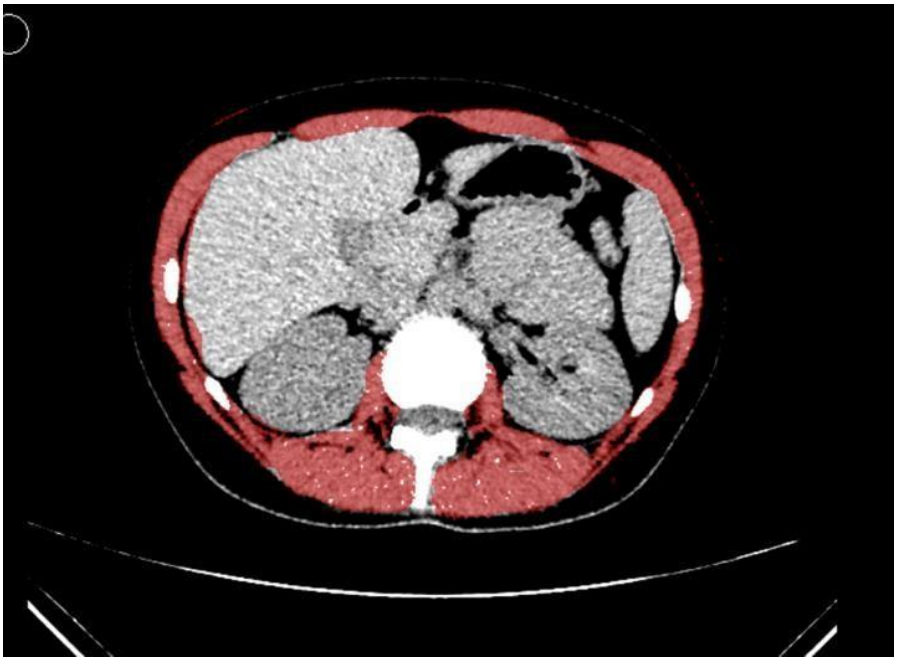

Fig. 3. 60-year-old man with sarcopenia. CT images extending inferiorly from L3 were evaluated automatically. After application of a predefined HU threshold, the boundaries were corrected manually when necessary. CT, computed tomography; HU, Hounsfield unit.

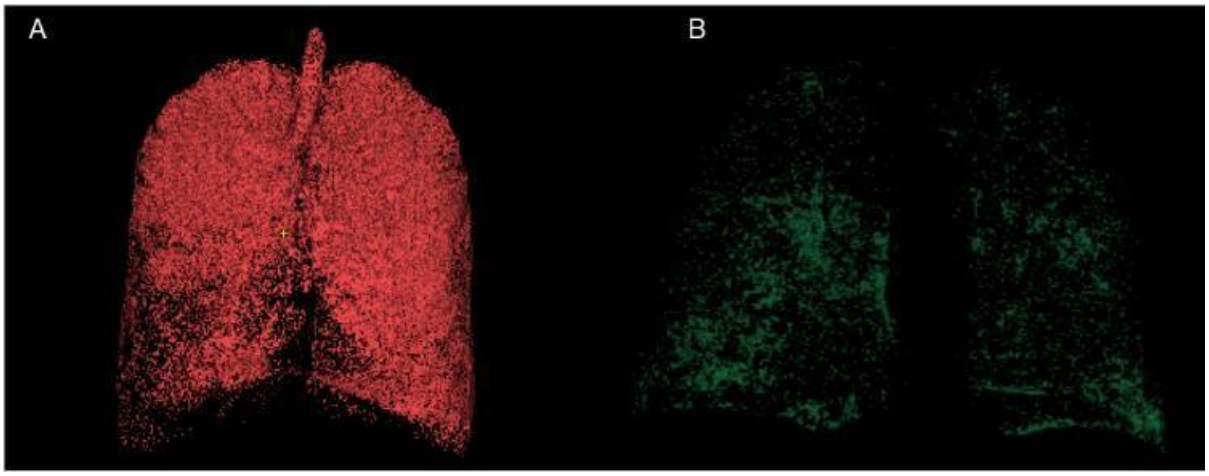


Fig. 4. Examples of pulmonary densitometry analysis for the diagnosis of ILAs and emphysema using reconstruction and automated detection. A, Severe emphysema in a 65-year-old man. B, Moderate ILAs in a 65-year-old man. ILAs, interstitial lung abnormalities.

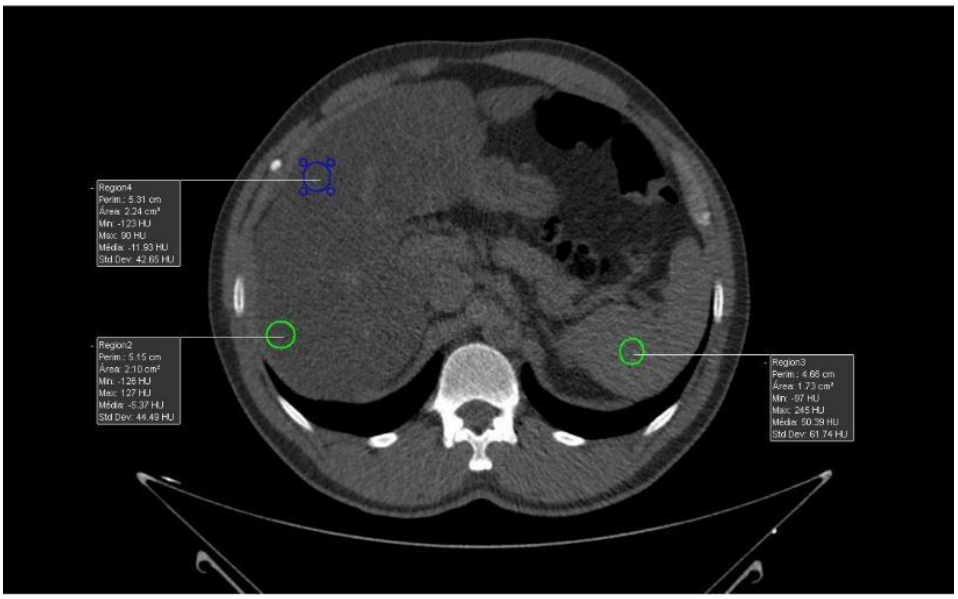


Fig. 5. 65-year-old man with hepatic steatosis. Attenuation of the liver (regions 2 and 4) and spleen (region 3) was assessed using region of interest tools in post-processing programs. CT, computed tomography.

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## 5. CONCLUSÕES

Nesse estudo retrospectivo, a análise expandida e quantificada das tomografias de tórax de baixa dose durante estudo de rastreamento de câncer de pulmão realizado no Brasil, identificou a presença de seis comorbidades relacionadas ao tabagismo. Ainda, novos diagnósticos de CAC, enfisema e osteoporose, foram realizados, o que possibilita o tratamento precoce de doenças antes desconhecidas pelos pacientes participantes.

O presente trabalho também demonstrou a importância de realizar mais estudos como esse em países em desenvolvimento, onde as taxas de mortalidade e incidência de câncer de pulmão, assim como a prevalência de tabagistas, ainda é alta e necessita de mais incentivos no sistema público de saúde.

Dessa forma, os resultados mostram a alta prevalência de doenças tabaco-relacionadas em estudos de rastreamento, e a importância de uma avaliação integrada da TC como parte dos estudos. A identificação dessas comorbidades, oferece oportunidade para um tratamento precoce, assertivo e eficaz, aumentando a chance de um prognóstico favorável. Além de, agregar valor aos estudos de rastreamento de câncer de pulmão.

## 6. CONSIDERAÇÕES FINAIS

O presente estudo faz parte de um projeto maior intitulado “Protocolo Check Lung: Agregando valor ao rastreamento de câncer de pulmão por Tomografia Computadorizada.**”,** aprovado pelos Comitês de Ética em Pesquisa (CEP) da UFCSPA (Parecer N° 4.639.969) e da Irmandade da Santa Casa de Misericórdia de Porto Alegre - ISCMPA (Parecer Nº 4.444.927). Do grande projeto, Protocolo Check Lung: Agregando valor ao rastreamento de câncer de pulmão por Tomografia Computadorizada, está sendo realizado um estudo prospectivo para identificação de comorbidades relacionadas ao tabagismo durante o estudo de rastreamento de câncer de pulmão em andamento no Hospital Pavilhão Pereira Filho (ISCMPA).

O Pavilhão Pereira Filho é um dos hospitais do complexo da Santa Casa referência na América Latina em pneumologia e cirurgia torácica, além de promover assistência qualificada em prevenção, diagnóstico, tratamento e reabilitação do paciente. O hospital possui ampla atuação no ensino de graduação, pós-graduação e em pesquisa, essencial para a continuidade desse estudo.

O presente estudo possibilitou apresentar dados que comprovam a importância da avaliação das comorbidades relacionadas ao tabagismo integrada com os estudos de rastreamento de câncer de pulmão, utilizando o mesmo método e exame diagnóstico, a TC de tórax de baixa dose. Nesse sentido, a perspectiva é dar continuidade ao estudo prospectivo em andamento, visando oferecer aos pacientes participantes, a oportunidade de tratamento precoce e eficaz para as comorbidades identificadas no estudo de rastreamento.

## 7. BIOGRAFIA

Minha trajetória acadêmica começa na UFCSPA, local onde iniciei e concluí a graduação em biomedicina, em dezembro de 2019. Durante o curso, realizei iniciação científica na UFRGS entre 2016 e 2019, no laboratório de psicofarmacologia e comportamento (LAPCOM), local onde foi realizado parte do meu trabalho de conclusão de curso titulado: “Efeito tipo-ansiolítico da liraglutida em peixes-zebra”. Durante a iniciação científica apresentei dois trabalhos no Salão de Iniciação Científica da UFRGS, são eles: “Efeitos da N-acetilcisteína micronizada nos testes de tanque novo e claro/escuro em peixes-zebra” (2017), e “N-acetilcisteína previne ansiedade e peroxidação lipídica induzido pela abstinência ao álcool em peixe-zebra” (2018).

No último ano da graduação, realizei dois estágios curriculares em análises patológicas (Policlínica Militar de Porto Alegre. PMPA.) e Imagenologia (Hospital Unimed Noroeste), e um estágio extracurricular (curso de extensão) em técnicas de ressonância magnética (Hospital São Lucas-PUC-RS).

Em março de 2021 ingressei no Programa de Pós-Graduação em Patologia da UFCSPA como aluna de mestrado. Durante minha trajetória na pós-graduação, assim como na preparação do projeto de pesquisa, participei de alguns congressos e jornadas apresentando um pouco da pesquisa que estava desenvolvendo. No Congresso Brasileiro de Pneumologia e Tisiologia – SBPT, recebemos o prêmio de primeiro lugar apresentando o trabalho: “Protocolo Check Lung: Agregando valor ao rastreamento de câncer de pulmão por Tomografia Computadorizada”. Em 2021 também apresentamos o na Jornada Paulista de Radiologia.

Ainda, contribuí com alguns artigos publicados durante o mestrado, sendo o primeiro citado o artigo da conclusão do mestrado. São eles:

- DE MATTOS, JULIANE NASCIMENTO; SANTIAGO ESCOVAR, CARLOS EUGÊNIO; ZEREU, MANUELA; RUBIN, ADALBERTO SPERB; CAMARGO, SPENCER MARCANTONIO; MOHAMMED, TAN-LUCIEN; DOS SANTOS, RICARDO SALES; VERMA, NUPUR; PENHA PEREIRA, DIANA; GUEDES PINTO, ERIQUE; MACHUCA, TIAGO; MEDEIROS, TÁSSIA MACHADO; HOCHHEGGER, BRUNO . Computed tomography on lung cancer screening is useful for adjuvant comorbidity diagnosis in developing countries. Erj Open Research, v. 8, p. 00061-2022, 2022.
- HOCHHEGGER, BRUNO; MATTOS, JULIANE; MARCHIORI, EDSON. Mosaic attenuation in a patient with COVID-19 pneumonia. Jornal Brasileiro de Pneumologia (Online), v. 47, p. e20200559, 2021.
- HOCHHEGGER, BRUNO; LONZETTI, LILIAN ; RUBIN, ADALBERTO ; DE MATTOS, JULIANE NASCIMENTO ; VERMA, NUPUR ; MOHAMMED, TAN-LUCIEN H ; PATEL, PRATIK P ; MARCHIORI, EDSON . Chest MRI with CT in the assessment of interstitial lung disease progression in patients with systemic sclerosis. RHEUMATOLOGY, 2022.
- HOCHHEGGER, BRUNO; MATTOS, JULIANE NASCIMENTO DE; MARCHIORI, EDSON. Pneumorrhachis: an uncommon finding in patients with COVID-19. Revista da Sociedade Brasileira de Medicina Tropical, 2021.

# 8. APÊNDICES

## 8.1 Artigos publicados

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

Juliane Nascimento de Mattos[1,2], Carlos Eugênio Santiago Escovar[3], Manuela Zereu[3], Adalberto Sperb Rubin[3], Spencer Marcantonio Camargo[3], Tan-Lucien Mohammed[4], Ricardo Sales dos Santos[5,6], Nupur Verma[4], Diana Penha Pereira[7], Erique Guedes Pinto[8], Tiago Machuca[4], Tássia Machado Medeiros[9] and Bruno Hochhegger[1,2,4,10]

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Shareable abstract (@ERSpublications)
Lung cancer screening is useful to facilitate comorbidity diagnosis in developing countries, providing opportunities for its prevention and treatment https://bit.ly/3KEdGuW

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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<br>Score 1: mild CAC (<1-cm calcification plaque)<br>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,ff] | >10 HU |
| Sarcopenia (SMA – L3 level)[¶¶] | <55 $cm^2/m^2$ (men)<br><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]; [ff]: 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].

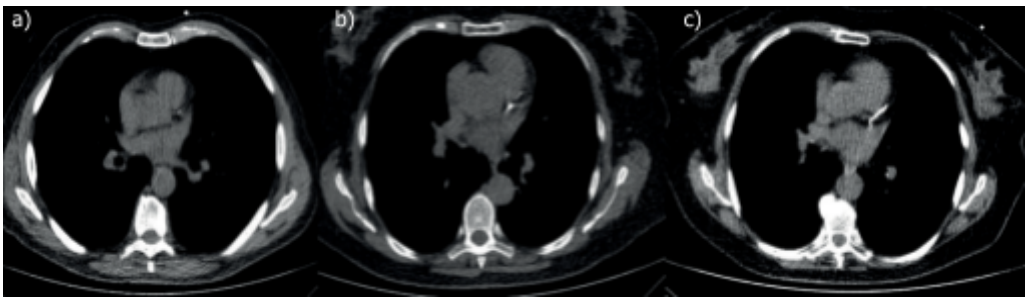


FIGURE 1 Examples of coronary artery calcification (CAC) analysis for the diagnosis of coronary artery disease from axial computed tomography images acquired without contrast. a) Mild CAC (score=1) in a woman aged 65 years. b) Moderate CAC (score=2) in a woman aged 55 years. c) Heavy CAC (score=3) in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

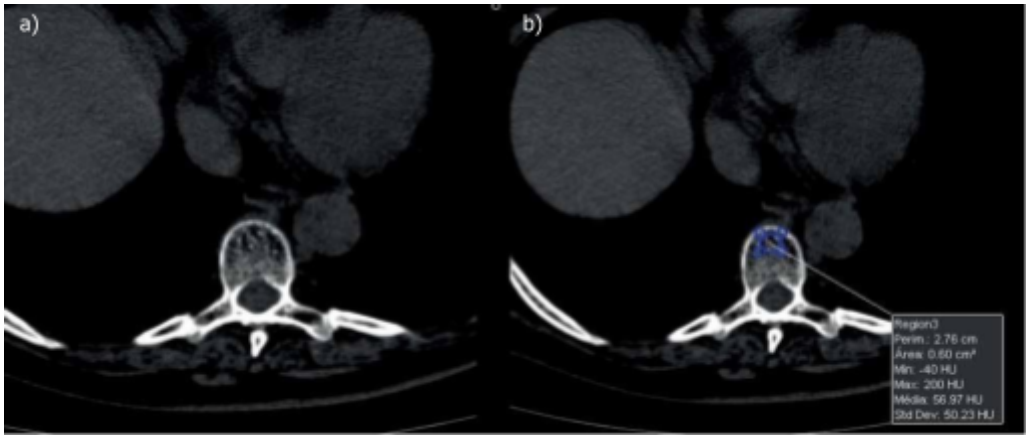


FIGURE 2 A 75-year-old woman with osteoporosis. a) Bone density was evaluated in the T12 region. b) A region of interest (area, 1.5–3 $cm^2$) was placed while avoiding cortical bone for the determination of bone density in Hounsfield units.

### *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).

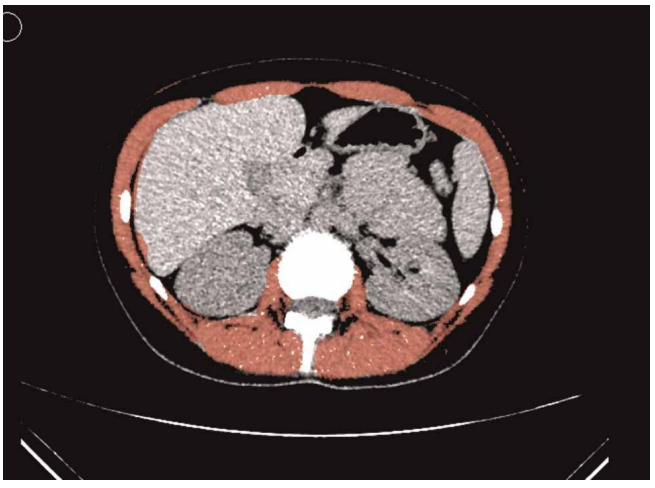

FIGURE 3 A 60-year-old man with sarcopenia. Computed tomography images extending inferiorly from L3 were evaluated automatically. After application of a predefined Hounsfield unit threshold, the boundaries were corrected manually when necessary.

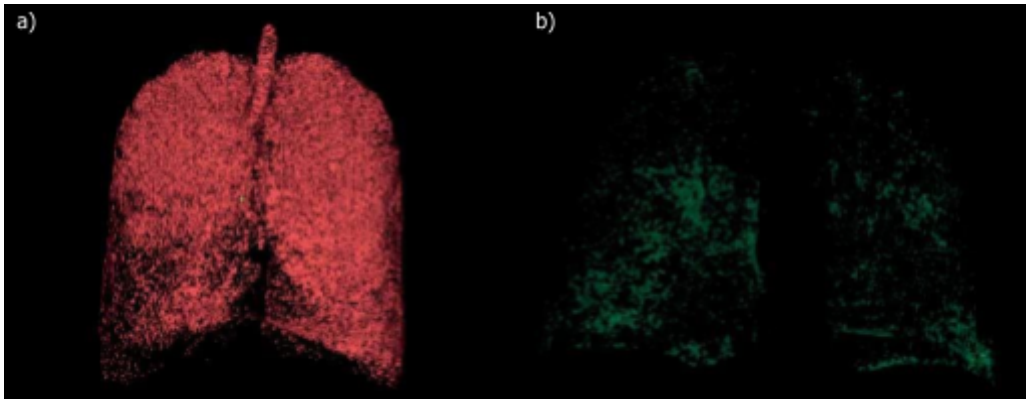


FIGURE 4 Examples of pulmonary densitometry analysis for the diagnosis of interstitial lung abnormalities (ILAs) and emphysema using reconstruction and automated detection. a) Severe emphysema in a 65-year-old man. b) Moderate ILAs in a 65-year-old man.

### *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

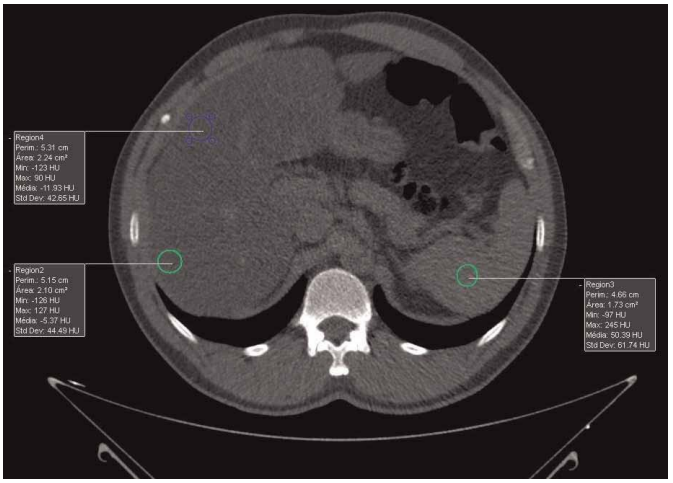


FIGURE 5 A 65-year-old man with hepatic steatosis. Attenuation of the liver (regions 2 and 4) and spleen (region 3) was assessed using region of interest tools in post-processing programs.

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.

Provenance: Submitted article, peer reviewed.

Conflict of interest: The authors declare no conflict of interest.

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# Atenuação em mosaico em paciente com pneumonia por COVID-19

Bruno Hochhegger[1]a, Juliane Mattos[1]a, Edson Marchiori[2]a

Mulher, 80 anos, sem história de tabagismo, asma ou outras doenças pulmonares prévias, procurou a emergência com queixas de febre, náuseas e intenso cansaço, sendo feito o diagnóstico de COVID-19 por RT-PCR. Sua $SpO_2$ em ar ambiente era de 85%. Após a alta, por dois meses e meio manteve dispneia a grandes e médios esforços, com avaliação cardiológica normal. Naquela época foi solicitada TC de tórax que mostrou padrão de atenuação em mosaico (PAM; Figuras 1A, 1B e 1C). Os cortes obtidos em expiração evidenciaram aprisionamento aéreo (Figuras 1D e 1E). A paciente tinha uma TC de tórax prévia, realizada em novembro de 2019 (dez meses antes da TC solicitada), que mostrava parênquima pulmonar normal (Figura 1F).

PAM é um padrão tomográfico no qual se observa áreas com diferentes valores de atenuação distribuídas difusamente no parênquima pulmonar. Pode ser resultado de doenças vasculares, doenças das pequenas vias aéreas e doenças parenquimatosas. Nossa paciente não apresentava alterações na vascularização pulmonar e cursava com aprisionamento aéreo, sendo então o comprometimento caracterizado como de pequenas vias aéreas. As principais doenças de pequenas vias aéreas que podem cursar com PAM são as bronquiolites, a pneumonite por hipersensibilidade e a asma brônquica.[1] O aprisionamento aéreo também tem sido descrito em pacientes em fase de recuperação de COVID-19, sendo que estudos histopatológicos demonstraram bronquiolite aguda e bronquiolite necrosante.[2]

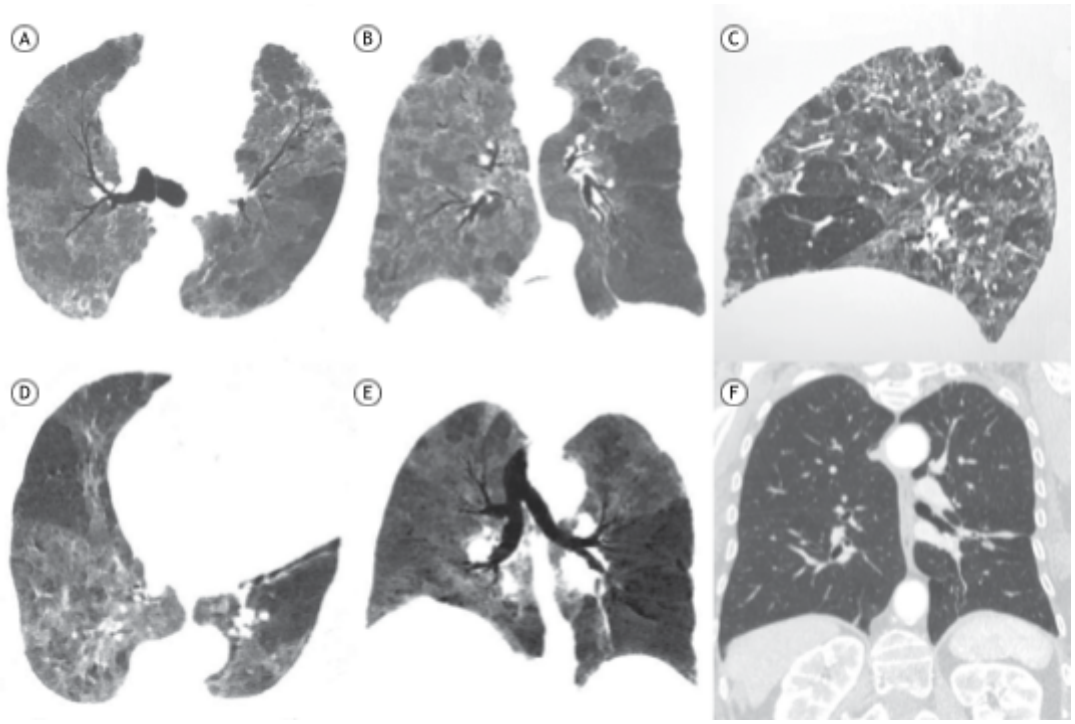


**Figura 1.** TC de tórax com reconstruções axial (em A), coronal (em B) e sagital (em C) demonstrando áreas de diferentes atenuações no parênquima pulmonar. A sequência em expiração (em D e E) evidenciou aprisionamento aéreo. Em F, TC de tórax realizada dez meses antes, mostrando parênquima pulmonar normal, exceto por pequena opacidade em faixa no terço médio do pulmão esquerdo.

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# Images in Infectious Diseases

## Pneumorrhachis: an uncommon finding in patients with COVID-19

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A 78-year-old man presented to the emergency department with a seven-day history of headache, fever, diffuse myalgias, dry cough, and dyspnea. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was diagnosed by SARS-CoV-2 RNA detection in nasopharyngeal samples. Chest computed tomography (CT) demonstrated predominantly peripheral ground-glass opacities in both lungs (**Figure 1A**), suggestive of a viral infection. The patient's cough markedly worsened during hospitalization. He experienced sudden onset anterior chest pain radiating to the neck, followed by dyspnea, after a severe coughing episode. The patient's peripheral oxygen saturation on room air was 88%. Repeat CT showed extensive subcutaneous emphysema dissecting the muscular planes of the cervical and dorsal regions, extending into the mediastinum and medullary canal (**Figures 1B-D**). He was treated with analgesics, cough suppressants, and supplemental oxygen through a nasal cannula, showing partial improvement.

Pneumorrhachis (PR) is an uncommon condition defined as the presence of air in the spinal canal, most often resulting from spinal cord injuries or instrumentation; but also occasionally reported in association with spontaneous pneumomediastinum, as in our case. Spontaneous pneumomediastinum and PR can occur when intra-alveolar pressure increases, as occurs with forceful coughing, leads to the rupture of the central pulmonary alveolus. Air can move into the perivascular interstitium and dissect through the fascial planes from the posterior mediastinum or retropharyngeal space through the neural foramina into the epidural space[1–3]. Spontaneous pneumomediastinum-associated PR is usually self-limiting, following a generally benign, conservatively managed course.

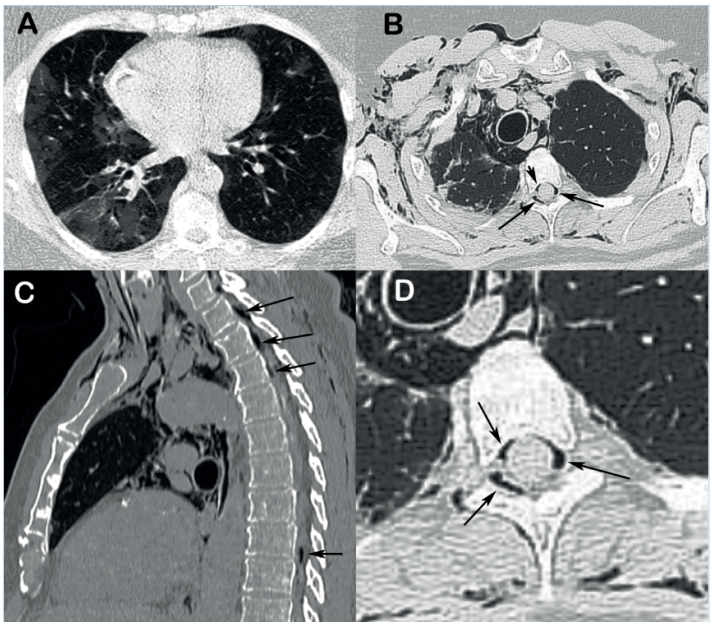


**FIGURE 1: (A)**, chest CT (axial reconstruction) showing right-sided predominant ground-glass opacities in both lungs. Chest CT with axial **(B)** and sagittal **(C)** reconstructions performed two weeks later, demonstrating subcutaneous emphysema, pneumomediastinum, and pneumorrhachis (arrows); **(D)**, spot film demonstrating a large amount of air within the spinal canal (arrows).

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**AUTHORS' CONTRIBUTION**

BH, JNM and EM: took part in conception of the manuscript and data acquisition. BH, JNM: contributed to the analysis and interpretation of data.EM: drafted the manuscript and reviewed the literature. All authors gave final approval of the version to be published.All authors contributed significantly to the work, and have read the manuscript and approved its submission.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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# Chest MRI with CT in the assessment of interstitial lung disease progression in patients with systemic sclerosis

**ORIGINAL RESEARCH**

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## Abstract

**Objective**: To describe the performance of CT and MRI in the assessment of the progression of interstitial lung disease (ILD) associated with systemic sclerosis (SSc) and demonstrate the correlations of MRI with pulmonary function test (PFT) and CT scores. **Methods:** This prospective single-center observational study included patients with SSc diagnoses and MR images were assessed visually using the Scleroderma Lung Study (SLS) I system. Differences in the median scores were assessed with t-test and the Wilcoxon rank-sum test. Pearson's and Spearman's Rank correlation coefficients were calculated to correlate imaging scores and PFT results. Using disease progression as the gold standard, we calculated the AUCs of the CT and MRI scores with Harrel's c-index. The best thresholds for the prediction of disease progression were determined by ROC curve analysis with maximum Youden's Index ($p < 0.05$). The sensitivity, specificity, PPV, and NPV of the scores were calculated. **Results:** The AUCs for MRI and CT scores were 0.86 (0.72–0.98; $p = 0.04$) and 0.83 (0.70–0.99; $p = 0.05$), respectively. CT and MRI scores correlated with FVC% (MR: r = -0.54, p =0.0045 - CT: r = -0.44; p =0.137) and DCO (MR: r = -0.39; p =0.007 - CT r = -0.36: p =0.006). The sensitivity, specificity, PPV, and NPV were 85%, 87.5%, 88.34% and 86.11% (MR score) and 84.21%, 82.35%, 84.14% and 82.4% (CT score). **Conclusions:** MRI scores from patients with SSc may be an alternative modality for the assessment of ILD progression in patients with SSc.

**Keywords:** interstitial lung disease; computed tomography; magnetic resonance imaging; idiopathic pulmonary fibrosis; systemic sclerosis.

**Key messages:**

- MRI, CT, and PFT results may aid the assessment of ILD progression in SSc patients.
- The MR method used in this study has the potential to predict SSc-ILD progress without radiation.

## Introduction

Lung involvement, including interstitial lung disease (ILD), is a leading cause of death among patients with systemic sclerosis (SSc) (1–3). The initiation of treatment early in the course of SSc-ILD may lead to improved clinical outcomes and is a predictor of significant lung function improvement, regardless of the drug used (4). For this reason, rigorous screening programs to facilitate the early diagnosis and treatment of SSc-ILD are of paramount importance (5).

The diagnostic tools used most frequently for ILD diagnosis in patients with SSc are high-resolution computed tomography (HRCT) and PFT (6). Due to its high degree of sensitivity, HRCT can be used to identify mild or early interstitial abnormalities of unknown clinical significance, which should prompt heightened surveillance for signs of progression. MRI of the lung has been demonstrated to be a feasible means of determining the presence of activity in patients with lung diseases; however, further research is needed before it can be established as an alternative to CT and PFT for the diagnosis and management of ILD. MRI has recently been established as a valuable diagnostic modality for ILD (7). Its ultrafast sequences and improved image quality, as well as the lack of ionizing radiation and versatile tissue characterization abilities, are among its advantages (8). To describe the performance of CT and MRI in the assessment of the progression of ILD associated with SSc. The secondary aim is to demonstrate the correlations of MRI with pulmonary function test and CT scores.

## Methods

### Patients

This single-center study conducted at Santa Casa de Misericórdia de Porto Alegre Hospital was approved by the institution's ethics committee (no. 1780557). Consecutive patients with SSc who were referred for chest HRCT between January 2015 and

December 2019 were included. The inclusion criteria were age ≥ 18 years, confirmed diagnosis of SSc based on the 2013 American College of Rheumatology and European League Against Rheumatism criteria. PFT and HRCT performed with standard parameters in the previous 1.5 months (6). Patients with claustrophobia were excluded.

Informed consent was applied to the participants describing the beneficials of the study, as well as the risks and all the researchers' responsibilities. The participants received the written informed consent.

Imaging technique

MRI was performed with a Magnetom Aera device (Siemens Healthcare) with an 18-channel anterior body coil and a 32-channel posterior spine coil. The patients were supine with their arms extended along the body and were moved into the device headfirst. Two datasets were acquired for this study. A T2-weighted turbo spin-echo sequence with fat suppression was obtained using the periodically rotated overlapping parallel lines with enhanced reconstruction (PROPELLER) technique, and more specifically the BLADE method, which is a PROPELLER-equivalent function of the Siemens Medical System. A T2-BLADE sequence was acquired during patients' free-breathing, with a respiratory navigator placed on the right at diaphragm level at end-normal expiration, using the following parameters: TR/TE = 2000/27 ms, flip angle = 150°, averages = 1, voxel size = 1.4 × 1.4 × 3 $mm^3$, and acquisition time = 4–8 min. For patients unable to adequately hold their breath, we used nasal-cannula oxygen delivery, patient hyperventilation, and fewer phase-encoding steps to reduce the sequence acquisition time.

HRCT was performed as part of diagnostic assessment using a 64-section scanner (Light Speed; GE Medical Systems, Milwaukee, WI, USA) during a single breath-hold

with standard acquisition parameters: 200 mA with automated dose reduction, 120 kV, pitch = 1, 0.5-s rotation time, 0.625-mm collimation, 400 × 400-mm field of view and 512 × 512 acquisition matrix. Pulmonary CT images were reconstructed using a soft filter to yield contiguous 0.625-mm axial sections from the apex of the lung to the diaphragm. Thin-section (1.25-mm) CT images were reconstructed every 1 mm using a high-spatial-resolution filter.

Image post-processing

Two independent radiologists (BH and MCB), each with 10 years of clinical experience, who were blinded to the CT and MRI findings reviewed the CT and MR images using a standard workstation (GE Healthcare). They also identified enlarged (short-axis transverse diameter > 10 mm) mediastinal lymph nodes and pleural and pericardial effusions. Pulmonary fibrosis, bronchial disease, and emphysema were evaluated using the CT images.

Scoring of CT findings

The severity of ILD was assessed visually and graded using the semi-quantitative SLS I system (9). According to this system, three zones of each lung were delineated using the aortic arch and pulmonary vein (upper, apex to the aortic arch; middle, aortic arch to the inferior pulmonary vein; lower, inferior pulmonary vein to diaphragm). For each zone, the severity of pure ground-glass opacity, lung fibrosis (including reticulation, bronchiectasis, and bronchiectasis), honeycombing, and emphysema were graded on a scale ranging from 0 to 4 (0 = absent, 1 = 1–25%, 2 = 26–50%, 3 = 51–75%, 4 = >75%). The two readers (BH and MCB) performed this assessment for all HRCT slices from the lung apex to base, scoring each of the six thoracic zones (range, 0–16). Total CT scores

ranged from 0 to 96 (Figure 1).

Scoring of MRI findings

MR images were assessed visually using the SLS I system (9). The extent of pulmonary T2 signal hyperintensity in the three lung zones were scored on a scale ranging from 0 to 4, as in the CT assessment (10,11). This is the MR extent score. The lung/muscle ratio was calculated by dividing the mean higher lung lesion signal intensity [in a region of interest (ROI) of 600–700 $mm_3$] by the mean paraspinal muscle signal intensity (in an ROI of 200–300 $mm_3$). Final MRI scores (range, 0–39) were obtained by multiplying the MRI extent score and MR muscle lung scores (12) (Figure 1)

Definition of disease progression

An attending rheumatologist followed patients via regular outpatient clinic appointments. The scans (CT and MR) were evaluated in time 0 and spirometry and clinic evaluation in time 12 (twelve months after). The progression of disease was defined as the worst of clinical symptoms and functional progression of disease ((≥10% reduction of forced vital capacity (FVC) or ≥15% reduction of lung diffusion of carbon monoxide (Dlco)). According to a previous study, although a change of ⩾10% FVC% predicted is clinically meaningful, exploratory analyses can be considered, as the lesser relative changes in FVC; marginal sustained reductions in FVC (5–10% as relative change), and changes in HRCT extent (13,14). Two rheumatologists, each with more than 10 years of experience, who were blinded to the lung MRI data evaluated each case separately. Four patients do not perform control DCO.

Statistical analysis

The statistical analyses were performed using SPSS software (ver. 18; SPSS Inc., Chicago, IL, USA). The Kolmogorov–Smirnov test was used to determine whether

variables were distributed normally. Continuous variables are expressed as means ± standard deviations or medians with interquartile ranges (IQRs). Discrete variables are expressed as frequencies with percentages. Differences in the median scores were assessed with the classical t-test and the Wilcoxon rank-sum test, which was conducted with Bonferroni correction. The differences of average were assessed with the paired t test with Bonferroni correction. Pearson's and Spearman's Rank correlation coefficients were calculated to investigate correlations between the imaging scores and PFT results. Using disease progression as the gold standard, we calculated the AUCs of the CT and MRI scores with Harrel's c-index. The best thresholds for the prediction of disease progression using the CT and MRI scores were determined by receiver operating characteristic curve analysis with maximum Youden's Index. The results are expressed in terms of AUCs. AUCs were compared using the method of DeLong (15). We used intra-class correlation coefficient (ICC). The ICC can take a value from 0 to 1, with 0 indicating no agreement and 1 almost perfect agreement. *p* values < 0.05 were considered significant. Cox proportional hazards model was used to describe hazard ratio of CT and MR score in relation with time to progression.

**Results**

The study sample comprised 36 patients [*n* = 32 (88.8%) women] with a mean age of 49 ± 8 years (Table 1). Patients were followed for 12 months, during this period 19 patients (19 women, age:51± 6 years) are categorized as progression disease. CT scores median, minimum and maximum were 5, 25 and 69. MR scores median, minimum and maximum were 3, 21 and 35. CT and MRI scores correlations with PFT are described. CT and MRI scores correlated with FVC% (MR: r = -0.54, p =0.0045 - CT: r = -0.44; p =0.137) and DCO (MR: r = -0.39; p =0.007 - CT r = -0.36: p =0.006) (Table 2). CT and

MR scores differed significantly between patients with stable and worsening lung involvement (Figure 2). Inter-reader agreement was substantial for CT and MRI scores [*ICC* = 0.66, 95% confidence interval (CI) 0.50–0.82 and *ICC* = 0.65, 95% CI 0.49–0.73,

respectively]. For multivariate analysis, the CT score and MR score were assessed (Table 3). A Bonferroni-corrected P value of <0.0083 (0.05/6) was considered significant. The AUCs for MRI and CT scores were 0.86 (0.72–0.98) and 0.83 (0.70–0.99), respectively (Figure 3). There is no statistical difference between CT score and MR score AUCs. Thresholds for optimal accuracy were 17 for the MRI score and 25 for the CT score. The sensitivity, specificity, positive predictive value, and negative predictive value were 85%, 87.5%, 88.34% and 86.11% in MR score and 84.21%, 82.35%, 84.14% and 82.4% in CT score.

**Discussion**

In this study, we demonstrated that MRI scores had similar accuracy in the prediction of SSc-ILD progression (according to functional test) and differed significantly between the stable disease and progression groups. In general, our findings suggest that MRI is a valuable modality for the evaluation of ILD in patients with SSc, with no radiation requirement.

Chest MRI can be useful for the diagnosis and assessment of thoracic pathologies due to technological advances such as the development of ultrafast sequences and improvement of acquisition speed and image quality (9,11,16,17). As it does not involve ionizing radiation exposure, MRI is an option for serial pulmonary parenchyma assessment. Moreover, immunomodulant treatment is indicated for active SSc-ILD, and the deleterious effects of radiation in immunocompromised patients have been well described (18,19). Recently, with the reduction in SSc-associated mortality related to renal crisis and lung fibrosis, experts and patients have become more concerned about long-term SSc-associated morbidities, especially possible associated malignancies, as

the incidence of malignant tumors is elevated in patients with SSc (20).

The use of chest MRI for SSc-ILD diagnosis has been described (11, 10, 16-18). Müller et al. (14) found that pulmonary MRI had 100% sensitivity, but only 60% specificity, in

the assessment of patients with SSc relative to chest CT. Pinal-Fernandez et al. (16) reported that MRI could be used to detect ILD with high degrees of sensitivity and specificity in patients with >0.5% parenchymal involvement, but that it was less sensitive than HRCT and its use led to the underestimation of disease extent. The use of MRI features as biomarkers of SSc-ILD worsening also has been examined. Gargani et al. demonstrated that MRI can be used to detect SSc-ILD independently of HRCT appearance and that it may be used to predict worsening lung involvement (7). The same study demonstrated a significant difference, in either STIR or T1 values, between normal and pathological ILD tissue areas, with HRCT as the gold standard and these results were supported by the significant correlations with other functional (%FVC, %TLC, %DLco) and radiological (HRCT SLS I score) parameters reflecting SScILD (7). The present study confirmed these findings and highlighted the use of MRI in such patient settings. However, more studies are needed to evaluate SLS I sQCT score adaptation to ILD-SSc MR assessment.

The limitations of this study include the single-center design and the inclusion of a limited number of patients. Further studies on larger patient samples are needed for a better MRI evaluation, especially in the assessment of lung fibrosis progression. The ILD assessment with MR part of the diagnostic path in SSc patients of the Authors' center because the patients did cardiac evaluation together. These same criteria were used in a previous study that compared lung MRI signal with HRCT and evaluated the role of MRI in predicting ILD progression (7). Also, we used manufacturer-specific T2-weighted MRI sequences to assess ILD, limiting the comparability of the data with that obtained using other manufacturers' devices. Another limitation in this study may be the non-use

of the Goh sQCT score (21), that is an important clinical study considering CT score (21).

In this study we didn´t find a statistically significant correlation between SLS1 CT score and % FVC may be due to the specific CT score. Also, our study demonstrates no statistically significant correlation of r= -0.44. The previous correlations of FVC: r= -0.50

(22); and FVC: r= -0.33 (23) has been described, but with larger number of patients included. We believe that absence of statistical correlation in part could be related with size of our sample.

The comparison between Goh sQCT and SLS1 scores could be studied in future studies. The Goh sQCT score is widely used and is a simple staging system for SSc-ILD as limited or extensive disease, based on simplified HRCT evaluation and FVC estimation, that provides more powerful prognostic information than either component in isolation (21). And similar to Goh's sQCT score, the SLS I score also evaluates the severity of pure ground-glass opacity, lung fibrosis (including reticulation, bronchiectasis, and bronchiectasis), honeycombing, and emphysema. In our study, we also considered the baselines values of %FVC, %TLC, %DLco. SLS, I score was used to assess the severity and extent of SSc-ILD with a high degree of reliability in several previous studies (13,24–31). Similar methods were also used (31,32). Also, considering the limited Dlco data of this study, the OMERACT definition of ILD progression could not be used for definition of ILD progression in all cases. However, this study considered the other aspects of OMERACT to define ILD progression as the change of ⩾10% FVC% and marginal sustained reductions in FVC (5–10% as relative change) (13,33). Other limitation is adaptation of SLS I to MR data, but this assessment was previous performed with acceptable results (16). Also, the difference of pixel size between MR and CT is a point that could have some bias, but as we are studying diffuse lung diseases in both methods the influence could be attenuated.

In conclusion, the quantitative MRI methods used in this study do not require radiation

exposure and have the potential to predict SSc-ILD progress, which would improve patient stratification according to the likelihood of benefitting from immunomodulatory therapy. The MR score has statistically significant correlations with PFTs.

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**Data availability statement:** All data are incorporated into the article and its online supplementary material.

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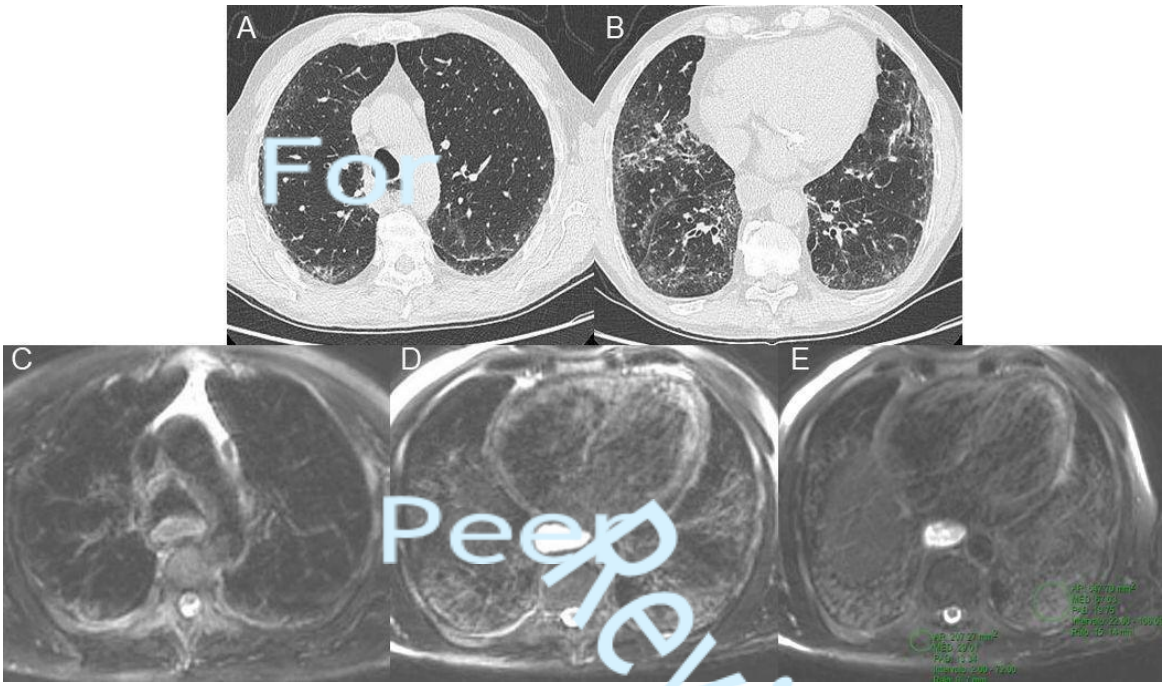


**Figure 1.** A 60-year-old woman with systemic sclerosis.

**A** and **B**, HRCT demonstrated extensive areas of stage-3 (50–75%) reticulation and ground-glass opacity in the middle and lower lung zones and incipient [stage 1 (0–25%)] ground-glass opacity and reticulation in the upper zones. The final CT score was 28. **C** and **D**, T2-weighted BLADE MRI demonstrated signal hyperintensity in the upper [stage 1 (0–25%)], middle, and lower [both stage 3 (50–75%)] zones of the pulmonary parenchyma. **E**, T2-weighted BLADE MRI assessment yielded a lung signal intensity score of 67 and a paraspinal muscle score of 29. The lung/muscle ratio was 2.3. The

final MRI score was 32.3.

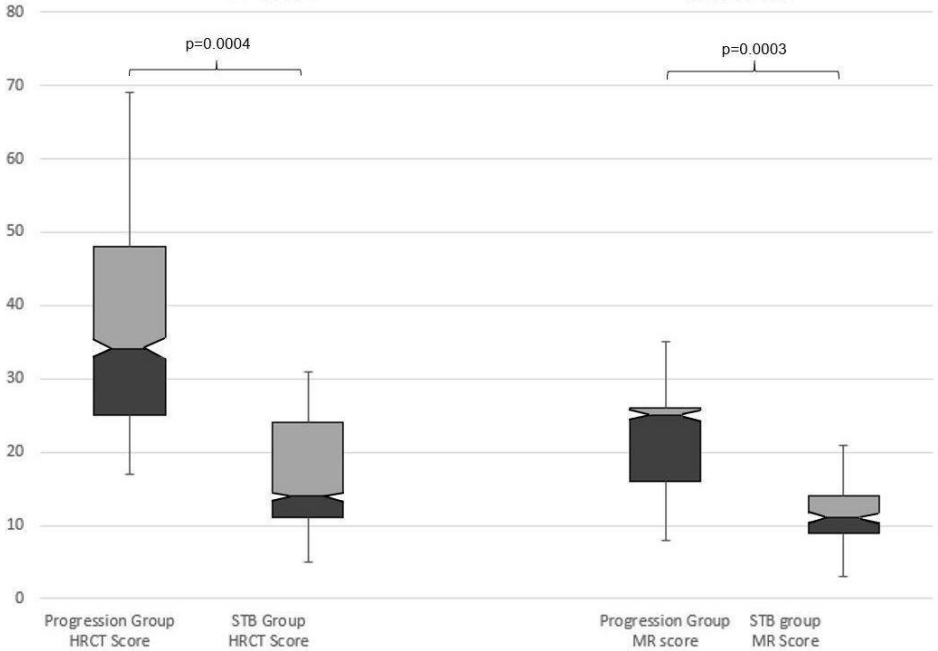


**Figure 2.** CT and MRI scores in the Progression Group and the Stable Group
High-resolution computed tomography (HRCT) and Magnetic Resonance (MR) Score were expressed as medians with interquartile ranges (IQRs) (*p-value* between groups for HRCT and MR score were 0.002 and < 0.0001, respectively).

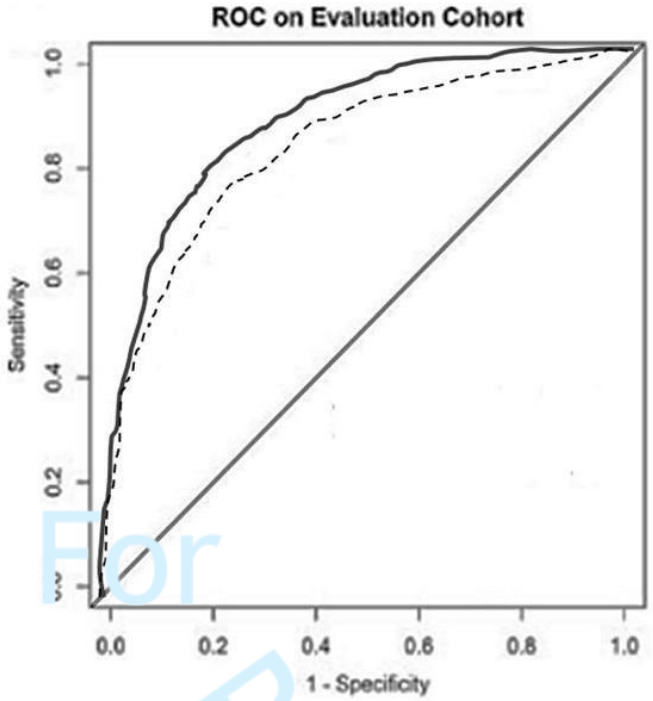


**Figure 3**. ROC curves for MRI scores and CT scores.

Receiver operator characteristic (ROC) curves for magnetic resonance imaging [MRI (continuous line)] scores and computed tomography [CT (dashed line)] scores. Area under curves (AUCs) were used to measure the accuracy of the CT and MRI scores. Thresholds for optimal accuracy were 17 for the MRI score and 25 for the CT score. The AUCs for MRI and CT scores were 0.86 (0.72–0.98) and 0.83 (0.70–0.99), respectively.

**Table 1.** Basal clinical characteristics of the study population

| Variable | Value | Progression | Stable |
|---|---|---|---|
| Female gender (*n*) | 32 | 19 | 13 |
| Age, years (median, IQR) | 49 (38–74) | 51 (41-74) | 47 (38-72) |
| Disease duration, years (median, IQR) | 4 (2–5) | 4.2 (3–5) | 4.8 (2-5) |
| Diffuse skin involvement (*n*) | 3 | 2 | 1 |
| Previous or ongoing smoking exposure (*n*) | 15 | 10 | 5 |
| Anti-nuclear antibodies positivity (*n*) | 36 | 19 | 13 |
| Anti-centromere antibodies positivity (*n*) | 12 | 8 | 4 |
| Anti-topoisomerase I antibodies positivity (*n*) | 12 | 7 | 5 |
| NVC Scleroderma pattern (*n*) | 23 | 21 | 20 |

IQR, interquartile ranges.

**Table 2.** Pulmonary function, CT, and MRI features of the patient groups.

| | MR Score | *p* values | CT score | *p* values |
|---|---|---|---|---|
| Forced vital capacity, % | -0.54 | *0.0004* | -0.44 | *0.137* |
| DLco, % | -0.39 | *0.0003* | -0.36 | *0.0005* |
| Total lung capacity, % | -0.48 | *0.0004* | -0.44 | *0.0005* |

CT, computed tomography; MRI, magnetic resonance imaging; DLco, diffusion of carbon monoxide.

**Table 3.** Performance of study measures in the prediction of worsening lung involvement (univariate and multivariate regression analyses).

| | Univariate HR (95% CI) | | Multivariate HR (95% CI) | |
|---|---|---|---|---|
| **CT Score** | *1.1 (1.002–1.162)* | *0.039* | 1.02 (0.981–1.14) | 0.298 |
| **MR Score** | *1.1 (1.005–1.128)* | *0.0005* | *1.28 (1.005–1.31)* | *0.0004* |

HR, hazard ratio; CI, confidence interval; CT, computed tomography; MRI, magnetic resonance imaging.

Rheumatology

**Decision Letter (RHE-21-1561.R4)**

**From:** editorial@rheumatology.org.uk

**To:** julianenmattos@gmail.com **CC:**

**Subject:** Rheumatology Manuscript RHE-21-1561.R4

**Body:** 22-Feb-2022

Rheumatology RHE-21-1561.R4: Chest MRI with CT in the assessment of interstitial lung disease progression in patients with systemic sclerosis.

Dear Ms Juliane de Mattos,

Thank you for submitting your manuscript to Rheumatology. The review process has now been completed and your paper has been accepted for publication pending style queries from the editorial office. Congratulations, we will be in touch with any queries soon.

We thank you in advance for your patience.

With kind regards,
The Rheumatology Editorial Office

**Date Sent:** 22-Feb-2022

Close Window

# 9. ANEXOS

## 9.1. Parecer do Comitê de Ética da UFCSPA e comprovante de artigo aceito.

IRMANDADE DA SANTA CASA DE MISERICORDIA DE PORTO ALEGRE - ISCMPA

## PARECER CONSUBSTANCIADO DO CEP

**DADOS DO PROJETO DE PESQUISA**

**Título da Pesquisa:** Protocolo Check Lung: Agregando valor ao rastreamento de câncer de pulmão por Tomografia Computadorizada.

**Pesquisador:** Bruno Hochhegger

**Área Temática:**

**Versão:** 1

**CAAE:** 39780620.3.0000.5335

**Instituição Proponente:** Irmandade da Santa Casa de Misericordia de Porto Alegre - ISCMPA

**Patrocinador Principal:** Financiamento Próprio

**DADOS DO PARECER**

**Número do Parecer:** 4.444.927

**Apresentação do Projeto:**

O rastreamento de câncer de pulmão (LCS, da sigla em inglês), por meio de tomografia computadorizada de tórax (TC), pode salvar vidas ao identificar tumores em estágio inicial. No entanto, a maioria dos participantes acabam morrendo de outras doenças relacionadas ao tabagismo durante os estudos. Ainda, o rastreamento para câncer de pulmão em TC de tórax de baixa dose, contém informações importantes sobre condições

relacionadas ao tabagismo que atualmente não são avaliadas sistematicamente. A identificação dessas comorbidades, utilizando o nosso protocolo

Check Lung, pode agregar valor aos estudos de triagem com impacto mínimo nos programas de LCS, além de melhorar a qualidade de vida aos participantes desses programas. Nesse sentido, o objetivo desse trabalho é determinar a prevalência de seis doenças comórbidas em TC de tórax de baixa dose, elegíveis para LCS e quantificar a sobrevida e a morte relacionadas.

**Objetivo da Pesquisa:**

Incorporar uma avaliação integral utilizando o protocolo de Check Lung, para o paciente que realiza o rastreamento de câncer de pulmão, através

TC de tórax de baixa dose para a realização do diagnóstico precoce.

Objetivo Secundário:

A) Avaliar aspectos normais acessados na TC de tórax;B) Realizar o rastreamento do câncer de

pulmão, avaliando doenças relacionadas como a
CAC;C) Realizar o rastreamento do câncer de pulmão, avaliando doenças relacionadas como osteoporose;D) Realizar o rastreamento do câncer de pulmão, avaliando doenças relacionadas como esteatose hepática;E) Realizar o rastreamento do câncer de pulmão, avaliando doenças relacionadas como doenças pulmonares;F) Realizar o rastreamento do câncer de pulmão, avaliando doenças relacionadas como sarcopenia;G) Quantificar a
sobrevida e mortalidade das doenças avaliadas em 12 meses.

**Avaliação dos Riscos e Benefícios:**
Riscos:
Os riscos para o paciente incluem o risco mínimo de perda de confidencialidade dos dados. Não haverá desconforto adicional aos sujeitos com coleta de exames. Todos os exames que serão utilizados já fazem parte da rotina de rastreamento de câncer de pulmão.
Benefícios:
Com os dados do estudo e se comprovando os benefícios da utilização de imagens pós-processadas para a identificação de comorbidades relacionadas à estudos de rastreamento de câncer de pulmão, pacientes futuros poderão também se beneficiar dessa técnica como forma de aumentar a segurança do procedimento.

**Comentários e Considerações sobre a Pesquisa:**
Um estudo que propõe salvar vidas e melhorar a qualidade de vida para os pacientes que fazem rastreamento de câncer de pulmão, identificando até seis comorbidades precoces, é de grande importância para a população. A avaliação integral dos pacientes que fazem o rastreamento oportuniza mais tempo de vida e tratamentos precoces.

**Considerações sobre os Termos de apresentação obrigatória:**
Apresentados e adequados.

**Conclusões ou Pendências e Lista de Inadequações:**
A pesquisa encontra-se de acordo com a Norma vigente Resolução 466/12 para pesquisa em seres humanos.

**Considerações Finais a critério do CEP:**
Após avaliação do protocolo acima descrito, o presente comitê não encontrou óbices quanto ao desenvolvimento do estudo em nossa Instituição e poderá ser iniciado a partir da data deste

parecer.

Obs.: 1 - O pesquisador responsável deve encaminhar à este CEP, Relatórios de Andamento dos Projetos desenvolvidos na ISCMPA. Relatórios Parciais (pesquisas com duração superior à 6 meses), Relatórios Finais (ao término da pesquisa) e os Resultados Obtidos (cópia da publicação).

2 – Para o início do projeto de pesquisa, o investigador deverá apresentar a chefia do serviço (onde será realizada a pesquisa), o Parecer Consubstanciado de aprovação do protocolo pelo Comitê de Ética.

**Este parecer foi elaborado baseado nos documentos abaixo relacionados:**

| Tipo Documento | Arquivo | Postagem | Autor | Situação |
|---|---|---|---|---|
| Informações Básicas do Projeto | PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1636500.pdf | 03/11/2020 10:39:45 | | Aceito |
| Outros | docs_ufcspa_cep.pdf | 03/11/2020 10:38:24 | Bruno Hochhegger | Aceito |
| Projeto Detalhado / Brochura Investigador | CHECK_LUNG_CEP.docx | 03/11/2020 10:37:33 | Bruno Hochhegger | Aceito |
| Outros | confidencialidade.pdf | 06/10/2020 08:49:44 | Bruno Hochhegger | Aceito |
| Outros | prontuarios.pdf | 06/10/2020 08:46:23 | Bruno Hochhegger | Aceito |
| Outros | isencao_de_onus.pdf | 06/10/2020 08:46:00 | Bruno Hochhegger | Aceito |
| Outros | inscricao_projeto.pdf | 06/10/2020 08:45:35 | Bruno Hochhegger | Aceito |
| Outros | formulario_inscricao_projeto_ass.pdf | 06/10/2020 08:42:04 | Bruno Hochhegger | Aceito |
| Solicitação registrada pelo CEP | declaracao_da_chefia_ass.pdf | 06/10/2020 08:41:06 | Bruno Hochhegger | Aceito |
| Folha de Rosto | folha_de_rosto_ass.pdf | 06/10/2020 08:40:12 | Bruno Hochhegger | Aceito |
| TCLE / Termos de Assentimento / Justificativa de Ausência | TCLE_rastreamento_de_cancer_de_pulmao.pdf | 30/09/2020 09:14:00 | Bruno Hochhegger | Aceito |

**Situação do Parecer:**
Aprovado

**Necessita Apreciação da CONEP:**
Não

PORTO ALEGRE, 07 de Dezembro de 2020

**Assinado por:**
**Claudio Marcel Berdún Stadñik**
**(Coordenador(a))**

UNIVERSIDADE FEDERAL DE CIÊNCIAS DA SAÚDE DE PORTO ALEGRE

# PARECER CONSUBSTANCIADO DO CEP

**Elaborado pela Instituição Coparticipante**

**DADOS DO PROJETO DE PESQUISA**

**Título da Pesquisa:** Protocolo Check Lung: Agregando valor ao rastreamento de câncer de pulmão por Tomografia Computadorizada.

**Pesquisador:** Bruno Hochhegger

**Área Temática:**

**Versão:** 2

**CAAE:** 39780620.3.3001.5345

**Instituição Proponente:** Universidade Federal de Ciências da Saúde de Porto Alegre

**Patrocinador Principal:** Financiamento Próprio

**DADOS DO PARECER**

**Número do Parecer:** 4.639.969

**Apresentação do Projeto:**

As informações elencadas neste campo foram retiradas do arquivo Informações Básicas da Pesquisa (PB_INFORMAÇOES_BÁSICAS_DO_PROJETO, DE 17/03/2021).

O rastreamento de câncer de pulmão (LCS, da sigla em inglês), por meio de tomografia computadorizada de tórax (TC), pode salvar vidas ao
identificar tumores em estágio inicial. No entanto, a maioria dos participantes acabam morrendo de outras doenças relacionadas ao tabagismo
durante os estudos. Ainda, o rastreamento para câncer de pulmão em TC de tórax de baixa dose, contém informações importantes sobre condições
relacionadas ao tabagismo que atualmente não são avaliadas sistematicamente. A identificação dessas comorbidades, utilizando o nosso protocolo
Check Lung, pode agregar valor aos estudos de triagem com impacto mínimo nos programas de LCS, além de melhorar a qualidade de vida aos
participantes desses programas. Nesse sentido, o objetivo desse trabalho é determinar a prevalência de seis doenças comórbidas em TC de tórax
de baixa dose, elegíveis para LCS e quantificar a sobrevida e a morte relacionadas.

**Objetivo da Pesquisa:**

As informações elencadas neste campo foram retiradas do arquivo Informações Básicas da Pesquisa (PB_INFORMAÇOES_BÁSICAS_DO_PROJETO, DE 17/03/2021).

Objetivo Primário:

Incorporar uma avaliação integral utilizando o protocolo de Check Lung, para o paciente que realiza o rastreamento de câncer de pulmão, através

TC de tórax de baixa dose para a realização do diagnóstico precoce.

Objetivo Secundário:

A) Avaliar aspectos normais acessados na TC de tórax;B) Realizar o rastreamento do câncer de pulmão, avaliando doenças relacionadas como a

CAC;C) Realizar o rastreamento do câncer de pulmão, avaliando doenças relacionadas como osteoporose;D) Realizar o rastreamento do câncer de

pulmão, avaliando doenças relacionadas como esteatose hepática;E) Realizar o rastreamento do câncer de pulmão, avaliando doenças relacionadas

como doenças pulmonares;F) Realizar o rastreamento do câncer de pulmão, avaliando doenças relacionadas como sarcopenia;G) Quantificar a

sobrevida e mortalidade das doenças avaliadas em 12 meses.

**Avaliação dos Riscos e Benefícios:**

As informações elencadas neste campo foram retiradas do arquivo Informações Básicas da Pesquisa (PB_INFORMAÇOES_BÁSICAS_DO_PROJETO, DE 17/03/2021).

Riscos:

Os riscos para o paciente incluem o risco mínimo de perda de confidencialidade dos dados. Não haverá desconforto adicional aos sujeitos com

coleta de exames. Todos os exames que serão utilizados já fazem parte da rotina de rastreamento de câncer de pulmão.

Benefícios:

Com os dados do estudo e se comprovando os benefícios da utilização de imagens pós-processadas para a identificação de comorbidades

relacionadas à estudos de rastreamento de câncer de pulmão, pacientes futuros poderão também se beneficiar dessa técnica como forma de

aumentar a segurança do procedimento.

**Comentários e Considerações sobre a Pesquisa:**

As informações elencadas neste campo foram retiradas do arquivo Informações Básicas da Pesquisa (PB_INFORMAÇOES_BÁSICAS_DO_PROJETO, DE 17/03/2021).

Este será um estudo prospectivo realizado com pacientes que possuem indicação clínica para rastreamento de câncer de pulmão no Hospital Santa
Casa de Misericórdia de Porto Alegre, onde serão avaliados TC de tórax de baixa dose (n=200) em uma única retenção máxima de respiração para
melhor resolução espacial, no período de outubro 2020 até outubro 2022.

**Considerações sobre os Termos de apresentação obrigatória:**

Vide campo “Conclusões ou Pendências e Lista de Inadequações”

**Recomendações:**

- O TCLE deve ser elaborado em duas vias e por isso, recomenda-se que, em futuros projetos, essa informação seja descrita dessa forma no TCLE.
- Em tempos de pandemia COVID-19, caso haja necessidade de adequação da metodologia, cronograma entre outros, deverá ser encaminhada "emenda", dentro da vigência do projeto.

**Conclusões ou Pendências e Lista de Inadequações:**

Trata-se de análise de resposta ao parecer pendente emitido pelo CEP quanto à versão 1 do projeto:

Após análise da resposta, a relatoria compreende que a solicitação foi atendida, não restando pendências. Assim, recomenda-se que o projeto seja considerado aprovado.

OBS:

Ressalta-se que cabe ao pesquisador responsável encaminhar os relatórios parciais e final da pesquisa, por meio da Plataforma Brasil, via notificação do tipo “relatório” para que sejam devidamente apreciadas no CEP, conforme Norma Operacional CNS nº 001/12, item XI.2.d.

**Considerações Finais a critério do CEP:**

De acordo com o parecer do Relator.

**Este parecer foi elaborado baseado nos documentos abaixo relacionados:**

| Tipo Documento | Arquivo | Postagem | Autor | Situação |
|---|---|---|---|---|
| Informações Básicas do Projeto | PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1677812.pdf | 17/03/2021 17:10:43 | | Aceito |
| TCLE / Termos de Assentimento / Justificativa de Ausência | TCLE_rastreamento_de_cancer_de_pulmao_corrigido.pdf | 17/03/2021 17:08:52 | Bruno Hochhegger | Aceito |
| Outros | carta_resposta_cep_ufcspa.pdf | 17/03/2021 17:07:18 | Bruno Hochhegger | Aceito |
| Outros | entrega_relatorio_ok.pdf | 23/02/2021 20:28:45 | Bruno Hochhegger | Aceito |
| Outros | docs_ufcspa_cep.pdf | 03/11/2020 10:38:24 | Bruno Hochhegger | Aceito |
| Projeto Detalhado / Brochura Investigador | CHECK_LUNG_CEP.docx | 03/11/2020 10:37:33 | Bruno Hochhegger | Aceito |
| Outros | confidencialidade.pdf | 06/10/2020 08:49:44 | Bruno Hochhegger | Aceito |
| Outros | prontuarios.pdf | 06/10/2020 08:46:23 | Bruno Hochhegger | Aceito |
| Outros | isencao_de_onus.pdf | 06/10/2020 08:46:00 | Bruno Hochhegger | Aceito |
| Outros | inscricao_projeto.pdf | 06/10/2020 08:45:35 | Bruno Hochhegger | Aceito |
| Outros | formulario_inscricao_projeto_ass.pdf | 06/10/2020 08:42:04 | Bruno Hochhegger | Aceito |
| TCLE / Termos de Assentimento / Justificativa de Ausência | TCLE_rastreamento_de_cancer_de_pulmao.pdf | 30/09/2020 09:14:00 | Bruno Hochhegger | Aceito |

**Situação do Parecer:**

Aprovado

**Necessita Apreciação da CONEP:**

Não

PORTO ALEGRE, 09 de Abril de 2021

**Assinado por:**
**Fernanda Bordignon Nunes**
**(Coordenador(a))**

ERJ Open Research

**Decision Letter (ERJOR-00061-2022.R2)**

**From:** erjor.editors@ersnet.org

**To:** julianenmattos@gmail.com

julianenmattos@gmail.com, eugenio.escovar@gmail.com, rubinadalberto@gmail.com, manuela.zereu@gmail.com, smcamargo07@gmail.com, MOHTAN@radiology.ufl.edu,

**CC:** rsbahia@hotmail.com, propulmao360@gmail.com, VERMNU@radiology.ufl.edu, dianapenha@gmail.com, ericguedespinto@gmail.com, machuca36@hotmail.com, tassiammd@hotmail.com, brunohochhegger@gmail.com

**Subject:** ERJ Open Research - Accept Decision on Manuscript ID ERJOR-00061-2022.R2

**Body:** 26-Apr-2022

Dear Ms. JULIANE DE MATTOS:

It is a pleasure to accept your manuscript entitled "CT on Lung Cancer Screening is useful for adjuvant comorbidity diagnosis in developing countries." in its current form for publication in ERJ Open Research.

The ERJ Open Research is a fully open access journal. A payment may be due before your article is published. Our partner CCC will contact the corresponding author about your open access options.

Some information on data sharing:
The ERS research journals encourage data sharing through the Dryad data repository (http://datadryad.org/). If you wish to deposit your dataset with Dryad, please ensure you specify that the dataset is linked to the ERJ Open Research and your manuscript ID: ERJOR-00061-2022.R2. The ERS has allocated funds to cover deposit fees, provided Dryad can link your submission to your article. For more information on data sharing please view our website (https://www.ersjournals.com/authors/data-sharing).

Thank you for your fine contribution. On behalf of the Editors of ERJ Open Research, we look forward to your continued contributions to the Journal.

Sincerely,

Dr. Esther Barreiro
Chief Editor - ERJ Open Research
ebarreiro@imim.es

Associate Professor Woo-Jung Song
Deputy Chief Editor - ERJ Open Research
swj0126@gmail.com

Dr. Torsten Blum
Associate Editor - ERJ Open Research
torsten-gerriet.blum@helios-kliniken.de, torstenblum@t-online.de

Editor Comments to Author:

Associate Editor
Comments to the Author:
The manuscript is ready for publication now - thanks a lot for all the work behind!

Reviewer(s)' Comments to Author:

**Date Sent:** 26-Apr-2022

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