ESCOLA DE MEDICINA
PROGRAMA DE PÓS-GRADUAÇÃO EM MEDICINA E CIÊNCIAS DA SAÚDE
DOUTORADO EM MEDICINA E CIÊNCIAS DA SAÚDE

STEPHAN PHILIP LEONHARDT ALTMAYER

# AVALIAÇÃO DOS ACHADOS DE TOMOGRAFIA COMPUTADORIZADA EM PACIENTES IMUNOCOMPETENTES COM COVID-19 COMPARADO A OUTRAS PNEUMONIAS VIRAIS: REVISÃO SISTEMÁTICA E META-ANÁLISE

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Tese de Doutorado pelo Programa de Pós-Graduação em Medicina e Ciências da Saúde da Escola de Medicina da Pontifícia Universidade Católica do Rio Grande do Sul

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## RESUMO

**Background**: Alguns trabalhos propuseram o uso da tomografia computadorizada (TC) de tórax para rastreio de paciente com suspeita de COVID-19. No entanto, os achados de imagem são inespecíficos e podem corresponder a qualquer outra etiologia de pneumonia viral. O objetivo desse trabalho foi de realizar uma revisão sistemática e meta-análise para comparar os achados da TC de COVID-19 a outras pneumonias virais.

**Métodos:** A Cochrane, EMBASE, MEDLINE foram pesquisados até 04 de abril de 2020 para estudos elegíveis. Critérios de elegibilidade incluíram estudos em pacientes imunocompetentes com pneumonia viral e amostra respiratória positiva para coronavírus ou outros tipos de pneumonia viral (não-COVID). Critérios de exclusão foram estudos não publicados em inglês ou com menos de 10 pacientes, inclusão de pacientes <16 anos de idade, e falta de confirmação laboratorial do diagnóstico para o agente etiológico. As prevalências combinadas dos achados foram calculadas e descritas com intervalos de confiança de 95% (IC 95%).

**Resultados:** Um total de 2263 estudos foram identificados, mas apenas 33 foram incluídos. Os principais achados de imagem para tanto COVID-19 quanto pneumonia não-COVID foram padrão predominante de vidro fosco (COVID-19, 0.42, IC 95% 0.28-0.55; não-COVID, 0.25; IC 95% 0.17-0.32) ou um padrão misto vidro fosco e consolidação (COVID-19, 0.37, IC 95% 0.17-0.56; não-COVID 0.46, 95% CI 0.35-0.58). A distribuição dos achados pulmonares foi predominantemente bilateral e envolvendo os lobos inferiores para ambas as etiologias. A COVID-19 teve uma maior prevalência de distribuição periférica e envolvimento dos lobos superiores e médios comparado a pneumonia não-COVID.

**Conclusão:** Apesar de uma maior prevalência de distribuição periférica e envolvimento de lobos médios e superiores, as pneumonias por coronavírus e outros vírus têm achados de imagem muito similares.



**Palavras-chave:** Coronavírus; tomografia computadorizada; TC; COVID-19; pneumonia viral.

## ABSTRACT

**Background:** Some authors have proposed the use of chest computed tomography (CT) to screen patients with suspected COVID-19; however, the imaging findings are nonspecific and could correspond to any other etiologic agent of viral pneumonia. The goal of this study was to carry out a systematic review and meta-analysis to compare the CT findings of COVID-19 compared to other viral pneumonia.

**Methods:** The Cochrane, EMBASE, and MEDLINE databases were searched through April 04, 2020 for eligible studies. Eligibility criteria included studies with immunocompetent patients presenting with viral pneumonia and a positive respiratory tract sample for coronavirus or other viral etiology (non-COVID). Exclusion criteria included studies not published in English or with less than 10 subjects, inclusion of patients <16 years of age, and lack of confirmatory laboratory diagnosis for viral etiology. Pooled prevalence of findings were calculated and described with 95% confidence intervals.

**Results:** A total of 2263 studies were identified, but only 33 met the inclusion criteria. The main CT finding for both COVID-19 and non-COVID viral pneumonia were a predominantly ground-glass opacity (GGO) pattern (COVID-19, 0.42, 95% CI 0.28-0.55; non-COVID, 0.25; 95% CI 0.17-0.32) or a mixed pattern of GGO and consolidation (COVID-19, 0.37, 95% CI 0.17-0.56; non-COVID 0.46, 95% CI 0.35-0.58). Distribution of lung opacities were predominantly bilateral and involved the lower lungs for both etiologies. COVID-19 had a higher prevalence of peripheral distribution, upper and middle lobe involvement compared to other viral pneumonia.

**Conclusion:** Despite the higher prevalence of peripheral distribution, involvement of upper and middle lobes, COVID-19 and non-COVID viral pneumonia had overlapping CT findings.



**Keywords:** Coronavirus; computed tomography; CT; COVID-19; viral pneumonia.

## LISTA DE ILUSTRAÇÕES

## LISTA DE TABELAS

## LISTA DE ABREVIATURAS

COVID-19 - *Coronavirus disease* 2019

FDA - *Federal Drug Administration*

MERS - Síndrome respiratória do Oriente Médio

OMS - Organização Mundial da Saúde

RT-PCR - Reação em cadeia de polimerase em tempo real

SARS-CoV-2 - *Severe acute respiratory syndrome coronavirus* 2

TC - Tomografia de tórax

**SUMÁRIO**

# 1 INTRODUÇÃO

No final de 2019, o aumento no número de casos de pneumonia na cidade de Wuhan na China levou à identificação de uma nova variante de coronavírus, que foi nomeado "*severe acute respiratory syndrome coronavirus 2*" (SARS-CoV-2) (1). A doença causada pelo SARS-CoV-2 foi nomeada como COVID-19 ("*coronavirus disease* 2019") pela Organização Mundial da Saúde (OMS) em fevereiro de 2020 (2). Após mais de 118 mil casos no mundo, a disseminação rápida do vírus levou a OMS a declarar oficialmente a COVID-19 uma pandemia (3). Em abril de 2021, mais de 140 milhões de casos de COVID-19 já foram diagnosticados globalmente, com mais de 3 milhões de mortes registradas (4). No mesmo período, o Brasil possui mais de 14 milhões de casos registrados e o número de fatalidades é de aproximadamente 380 mil (4).

Um dos maiores desafios da pandemia foi o de diagnosticar os casos suspeitos, já que o correto diagnóstico e isolamento são uma das principais estratégias para evitar a transmissão do vírus na comunidade. No entanto, o principal diagnóstico laboratorial para o coronavírus, a amplificação do RNA viral por reação em cadeia de polimerase em tempo real (RT-PCR), tem uma sensibilidade que varia de acordo com a qualidade da coleta e cronologia de sintomas (5). Considerando essa limitação do RT-PCR, alguns autores sugeriram o uso da tomografia computadorizada (TC) de tórax para rastreio de COVID-19 em paciente sintomáticos em uma tentativa de otimizar a capacidade de profissionais diagnosticarem (6). Entretanto, os achados de imagem de COVID-19 são muito similares às pneumonias por outros vírus. Nesse sentido, fica evidente a necessidade de se comparar os achados de imagem de pneumonias virais por coronavirus àquelas por outros vírus para determinar se o uso de TC de tórax como método diagnóstico de COVID-19 é plausível.

# 2 REVISÃO DA LITERATURA

## 2.1. Infecção e manifestações clínicas do SARS-CoV-2

*Coronaviridae* é uma família de vírus de RNA envelopados frequentemente associados a sintomas respiratórios, gastrointestinais e neurológicos (7). Os coronavírus mais comuns na prática clínica estão associados a infecção respiratória

leve em pacientes imunocompetentes. No entanto, o SARS-CoV-2 é o terceiro coronavírus associado a doença viral grave que tomou proporções globais nas últimas duas décadas (8). Os dois primeiros foram o SARS-CoV, que também se originou na China e resultou em uma pandemia em 2002-2003, e o coronavírus da síndrome respiratória do Oriente Médio (MERS) originado na península árabe em 2012 (9,10).

Acredita-se que os morcegos são os hospedeiros naturais do SARS-CoV-2, já que seu genoma demonstrou compatibilidade em 96% a um coronavírus identificado nos morcegos *Rhinolophus affinis* (11). Também se acreditou inicialmente que os pangolins (mamíferos que vivem em zonas tropicais da Ásia) poderiam ter sido o hospedeiro intermediário na transmissão do SARS-CoV-2 para humanos. No entanto, essa hipótese tem sido questionada na literatura (12), e a nossa compreensão da origem dos primeiros casos de SARS-CoV-2 ainda precisa ser melhor esclarecida. Independente da origem do vírus, a transmissão direta humano-humano se tornou o principal modo de infecção com a progressão do número de infectados. A transmissão ocorre principalmente pelo contato de gotículas respiratórias durante exposição próxima (menos de 2 metros) com pacientes infectados, por meio de tosse, secreção nasal ou saliva (7). Porém, transmissão por meio de contato com superfícies infectadas ou por meio de aerossóis (pequenas partículas respiratórias suspensas no ar) também pode ocorrer (13–15).

O período de maior transmissibilidade é nas fases iniciais da doença, especialmente nos dois primeiros dias antes do desenvolvimento de sintomas, quando a carga viral nas vias aéreas superiores está no seu máximo (16–18). A transmissibilidade diminui consideravelmente após 7 dias de sintomas (17,19,20). O período de incubação após infecção pelo vírus é de aproximadamente 5 dias, sendo que mais de 97% dos pacientes irão desenvolver sintomas em até 11 dias (21,22). A mediana (intervalo interquartil) de tempo entre desenvolvimento de sintomas e hospitalização é de 7 dias (3-9 dias) (23).

A infecção pelo SARS-CoV-2 pode ser assintomática ou causar uma variedade de sintomas de diferente gravidade, tal como sintomas leves de via aérea superior até pneumonia viral grave levando a morte (22,24). A proporção de pacientes assintomáticos é de aproximadamente 30-40% em estudos de testagem populacional, sendo que 80% destes acabam não desenvolvendo sintomas durante

um período de observação após testagem (25,26). Entre os pacientes sintomáticos, 80% desenvolvem sintomas leves, 15% desenvolvem sintomas graves (dispneia, hipoxemia, acometimento pulmonar >50% em exame de imagem), e 5% evoluem com insuficiência respiratória ou choque (27). Segundo um estudo de vigilância sanitária dos Estados Unidos com informação de 373.000 pacientes, os sintomas mais comuns são tosse (50.3%), febre (43.1%), cefaleia (34.4%), mialgia (36.1%), e falta de ar (28.5%) (28). No mesmo estudo, a perda de olfato ou paladar foi reportada em apenas 8.3% dos pacientes, enquanto uma revisão sistemática aponta um número de aproximadamente 50% (29). A prevalência de sintomas gastrointestinais (diarreia, dor abdominal, ou náusea) é de aproximadamente 18% em revisões sistemáticas (30).

## 2.2 Métodos diagnósticos para COVID-19

O método mais utilizado para o diagnóstico de COVID-19 é por meio do RT-PCR de amostras de *swab* nasal e orofaríngeo (5). O RNA viral pode ser detectado na via aérea superior até mesmo antes do desenvolvimento de sintomas, mas o pico de RNA em via aérea superior ocorre dentro da primeira semana após início dos sintomas e começa a decair com o tempo, especialmente após a terceira semana de início de sintomas (Figura 1)(5). Em alguns casos, o RNA viral pode ser detectado por RT-PCR mesmo após 3 semanas do primeiro teste positivo, o que não significa que o vírus ainda está ativo ou que o paciente é transmissor da doença (19). Uma revisão e meta-análise demonstrou a importância do tempo de sintomas para a sensibilidade do RT-PCR. A taxa de falso negativo no primeiro dia de sintomas encontrada foi de 38%, enquanto a mesma taxa no terceiro e quarto dia de sintomas foi de aproximadamente 20% (31). Com o passar dos dias essa taxa tende a aumentar, atingindo mais de 60% após a segunda semana de sintomas (31). A acurácia do teste depende não apenas da temporalidade dos sintomas, como também do local que a amostra é coletada. Em um estudo com 205 casos de infecção por COVID-19 confirmados, a taxa de detecção com RT-PCR foi de 93% no lavado broncoalveolar, 72% no escarro, 63% no *swab* nasal, e 32% no swab orofaríngeo (32). Dado que o RT-PCR é o “padrão-ouro” para o diagnóstico de COVID-19, a mensuração de sensibilidade e especificidade em estudos é complicada, já que para isso um

referencial de verdadeiro positivo precisa ser determinado. De um modo geral, a sensibilidade do RT-PCR na prática clínica quando utilizados múltiplos testes sucessivos como referencial gira em torno de 70-80% (31,33). A especificidade do teste realizado em condições de laboratório é de 100% (34), sendo raros os casos de falso positivos reportados, que provavelmente estão relacionados a contaminação de amostra (35,36).

Tabela 1. Resumo dos testes diagnósticos para SARS-CoV-2.

| **Teste** | **Uso clínico** | **Material** | **Performance e vantagens** |
|---|---|---|---|
| RT-PCR | Diagnóstico primeira semana de sintomas | *Swab* nasal ou orofaríngeo | - Alta sensibilidade de especificidade se bem coletado na fase inicial<br>- Sensibilidade aproximada de 70-80%<br>- Falso positivo raros |
| Sorologia (IgM, IgG) | Diagnóstico após 7 dias de sintomas; rastreio de imunidade na população | Sangue | - Sensibilidade altamente sensível ao tempo de sintomas (melhor após 5-7 dias)<br>- Especificidade >95% |
| Antígeno | Diagnóstico primeira semana de sintomas | *Swab* nasal ou orofaríngeo | - Sensibilidade menor que RT-PCR<br>- Alta especificidade<br>- Baixo custo, resultado rápido |

A detecção de antígenos virais é uma alternativa ao RT-PCR na fase inicial da doença em que a replicação viral é máxima. A principal vantagem é que são testes rápidos ("*point-of-care*"), sendo especialmente recomendados quando o tempo para o resultado do RT-PCR é muito longo ou para rastreio em populações de risco (37,38). A sensibilidade dos testes antigênicos atualmente aprovados pelo *Federal Drug Administration* (FDA) é de 84-100% (comparado ao RT-PCR), sendo que a especificidade é compatível com a do RT-PCR (37). No entanto, uma revisão sistemática recente incluindo estudos clínicos demonstrou uma sensibilidade média

de 56.2% (IC 95% 29.5 – 79.8%), mas a variabilidade entre os estudos foi muito grande (39). Portanto, quando a probabilidade pré-teste é grande e o teste antigênico é negativo, o RT-PCR se torna indispensável.

O teste sorológico com a detecção de anticorpos contra o SARS-CoV-2 também é utilizado na prática clínica. Esse método é especialmente utilizado em pacientes com sintomas leves ou moderados que se apresentam após as primeiras 2 semanas de sintomas (5). Apesar de relatos de detecção de IgM e IgG ocorrer tão cedo quanto o quarto dia de sintomas, os níveis de anticorpos se aproximam de seu pico próximo da segunda e terceira semana de sintomas (40). A detecção de anticorpos também pode ser utilizada em conjunto com PCR para otimizar a taxa de detecção em pacientes testados após 5-7 dias de sintomas (41). Assim como os testes antigênicos, muitos testes rápidos "*point-of-care*" foram desenvolvidos e aprovados para uso de emergência pelo FDA.

### 2.3 Valor da tomografia computadorizada de tórax em COVID-19

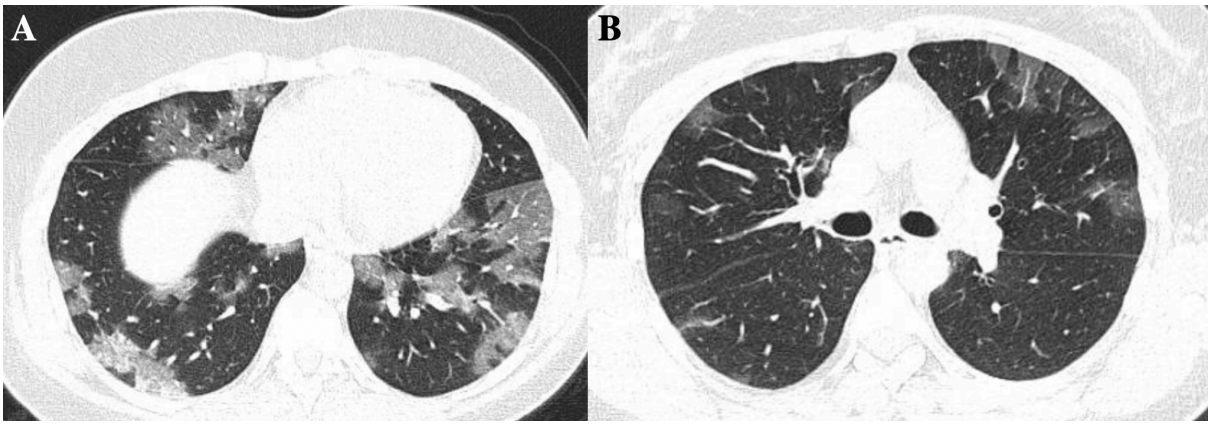
Considerando que nenhum teste laboratorial de COVID-19 é capaz de detectar 100% dos casos de infecção por SARS-CoV-2, nem mesmo o RT-PCR que é o padrão-ouro, alguns autores começaram a sugerir que a tomografia computadorizada (TC) de tórax fosse utilizada como método de rastreio para COVID-19 (6). A recomendação mais antiga nesse sentido surgiu com um dos primeiros trabalhos correlacionando TC de tórax e RT-PCR para COVID-19 por Ai et al (6). O racional dessa recomendação era o fato que a TC de tórax foi capaz de demonstrar alterações no parênquima pulmonar em pacientes com síndrome viral mais vezes (88%) que o RT-PCR foi positivo (59%). No entanto, a metodologia desse estudo pode ser questionada. Os autores incluíram um total de 1014 pacientes com síndrome viral aguda internados em Wuhan, China. Eles consideraram que todos estes pacientes eram "verdadeiros positivos", mesmo que o RT-PCR (o teste padrão-ouro) fosse negativo. Apenas 601 dos 1014 (59%) pacientes incluídos tiveram RT-PCR positivo, enquanto 888 dos 1014 tiveram TC positiva (88%). No entanto, sabemos que o SARS-CoV-2 é apenas um entre uma diversidade de vírus capaz de gerar os sintomas clássicos de uma síndrome gripal, sendo que a pandemia ocorreu simultaneamente

à sazonalidade do Influenza H1N1. Os autores não realizaram painel viral em pacientes com o RT-PCR negativo para ter certeza de que eles não estavam infectados com outro vírus (Influenza H1N1, adenovírus, etc.). Portanto, a referência "padrão-ouro" na análise dos autores foi uma apresentação de síndrome gripal aguda na cidade de Wuhan. Os pacientes com esse padrão, RT-PCR negativo, e TC de tórax "positiva" foram considerados verdadeiros positivos.

Além da limitação metodológica na definição do que seria a referência de "verdadeiro positivo", o segundo problema está na definição do que é uma TC positiva. No estudo de Ai e colaboradores, os achados mais comuns foram a presença de opacidades em vidro fosco (409/888, 46%), consolidação (447/888, 50%), espessamento de septos interlobulares (8/888, 1%) e lesões nodulares (24/888, 3%) (6). Outros trabalhos reportaram os mesmos achados, geralmente acometendo os pulmões de modo preferencialmente bilateral, periférico, e com predominância de envolvimento de lobos inferiores (Figura 1) (42–51). Sabe-se que estes achados são comuns em pneumonias virais, até mesmo bacterianas, de qualquer etiologia. Tais achados também são encontrados em pneumonia virais por Influenza H1N1 (Figura 2), adenovírus, e até mesmo doenças pulmonares não-infecciosas (52–75)(76).

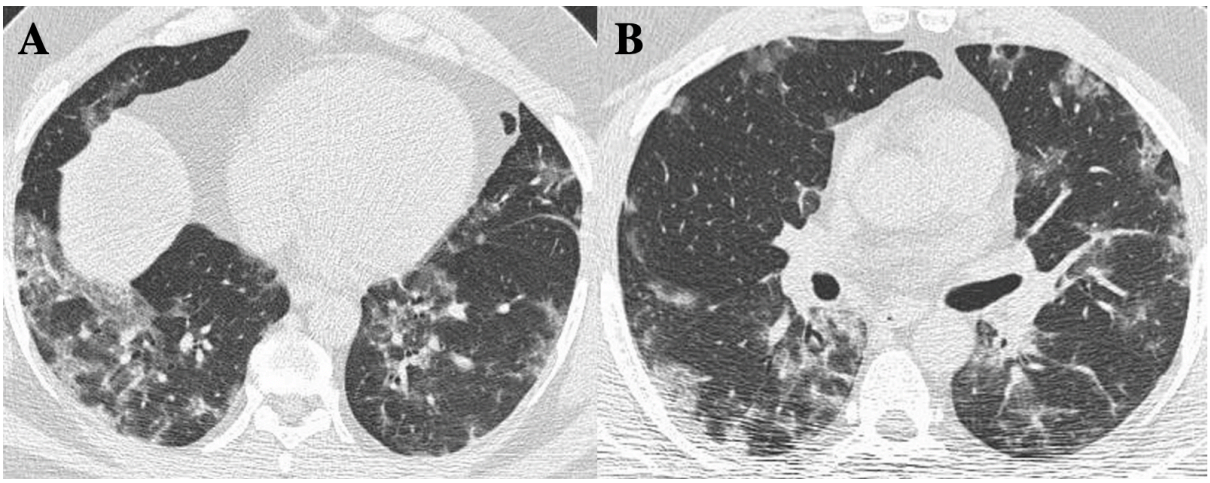
Dado, portanto, que nenhum achado positivo ou negativo na tomografia de tórax pode diagnosticar ou descartar a possibilidade de COVID-19, a *American College of Radiology* e a *British Society of Thoracic Imaging* não recomendam o uso de TC de tórax para o rastreio ou confirmação diagnóstica (77,78). Essa recomendação é apoiada pelo presente trabalho que demonstrou que os achados tomográficos mais comuns encontrados em COVID-19 se sobrepõem àqueles de outras pneumonias não-COVID. Além disso, uma recente meta-análise da acurácia diagnóstica pela Cochrane apontou uma sensibilidade de 89.9% (IC 95%, 85.7 - 92.9%) e especificidade de 61.1% (IC 95%, 42.3 – 77.1%) da TC de tórax em COVID-19 (79).

*Figura 1. Mulher de 50 anos com achados de TC típicas para COVID-19, diagnóstico confirmado por RT-PCR.*




(A, B) Tomografia de tórax em corte axial demonstrando opacidades em vidro-fosco bilaterais e periféricas com espessamento de septos interlobulares (pavimentação em mosaico), predominando em lobos inferiores.

*Figura 2. Homem de 42 anos com diagnósticos confirmado de H1N1.*




(A, B) Tomografia de tórax em corte axial demonstrando múltiplas opacidades em vidro-fosco periféricas e bilaterais, associadas a espessamento de septos interlobulares.

## 2.4. Achados da tomografia computadorizada tórax em pneumonias virais não-COVID

Os achados de imagem de pneumonias virais por outros vírus são bem heterogêneos e alguns entre os mais comuns em adultos estão demonstrados na Tabela 2 (80,81). Influenza A é um dos principais diagnósticos diferenciais de COVID-19, não só porque é a etiologia viral de pneumonia mais comum em adultos

imunocompetentes, mas também porque os achados de imagem são muito parecidos com o do coronavírus (opacidades em vidro fosco e/ou consolidações multifocais, bilateral, predominantemente periféricas) (81). Portanto, Influenza A acaba sendo um dos principais diagnósticos diferenciais em pacientes adultos imunocompetentes que se apresentam com síndrome gripal. Os achados de imagem dos outros vírus aqui descritos também envolvem uma parcela de pacientes imunocomprometidos, pois são raros os estudos de outros vírus – com a exceção de Adenovírus e Influenza – que envolveram apenas pacientes sem imunossupressão.

Os achados de Parainfluenza e Vírus Sincicial Respiratório são parecidos, consistindo em opacidades em vidro fosco e/ou consolidações multifocais e também nódulos centrolobulares (80–83). O Metapneumovírus humano é mais frequentemente encontrado em humanos com imunossupressão ou idade avançada, apresentando-se com opacidades multifocais em vidro fosco e/ou consolidações bilaterais, além de nódulos centrolobulares (84,85). Infeções por adenovírus causam opacidades multifocais em vidro fosco frequentemente com consolidações associadas. Além disso, presença de nódulos centrolobulares e espessamento de paredes brônquicas também são reportados (67,72). Por último, as pneumonias virais por herpes simples e citomegalovírus, que são muito mais frequentes em pacientes imunossuprimidos, podem se apresentar com opacidades em vidro fosco e consolidações multifocais, opacidades reticulares, nódulos centrolobulares, e também opacidades com sinal do halo (86–88).

Tabela 2. Resumo dos achados de imagem das pneumonias virais por coronavírus e outros vírus.

| **Etiologia** | **Vidro fosco e/ou consolidação** | **Opacidades nodulares** | **Espessamento septo interlobular** | **Espessamento de paredes brônquicas** |
|---|---|---|---|---|
| Coronavírus | +++ | + | +++ | ... |
| Influenza A | +++ | + | + | ... |
| Parainfluenza | +++ | ++ | ... | + |
| VSR | +++ | ++ | ... | + |
| MPVh | +++ | +++ | ... | ... |
| Adenovírus | +++ | + | ... | ++ |

| | | | | |
|---|---|---|---|---|
| CMV | ++ | ++ | ++ | ... |
| HSV | ++ | + | + | ... |

VSR, Vírus Sincicial Respiratório; MPVh, Metapneumovírus humano; CMV, Citomegalovírus; HSV, Herpes simples vírus.

Sinal de “+” indica a frequência dos achados, sendo “+” menos frequente e “+++” mais frequente.

“...” indica que os achados não são muito descritos para a etiologia viral específica

## 3 QUESTIONAMENTO

Os achados da TC de tórax em pacientes com COVID-19 são diferentes de pneumonias virais por outros vírus? **4 JUSTIFICATIVA**

Alguns estudos na literatura e muitos profissionais na prática clínica estão usando os achados típicos de COVID-19 na TC de tórax, isto é, padrão de opacidades em vidro-fosco, bilateral, periférico, acometendo especialmente lobos inferiores, como um achado patognomônico de pneumonia viral por COVID-19. No entanto, a literatura demonstra que pneumonias virais por outros vírus (e.g., H1N1, adenovírus) podem apresentar os mesmos achados de imagem. Portanto, os achados considerados "típicos" de COVID-19 não são específicos. Esse estudo tem como objetivo comparar os achados de TC de COVID-19 e outras pneumonias virais para sanar essa confusão observada tanto na literatura, quanto na prática clínica.

## 5 HIPÓTESE

Os achados tomográficos de COVID-19 não são diferentes das pneumonias virais por outros vírus.

# 6 OBJETIVOS

## 6.1 Objetivo Geral

Realizar uma revisão sistemática e meta-análise dos achados tomográficos de COVID-19 em pacientes imunocompetentes e comparar com aqueles de outras pneumonias virais.

## 6.2 Objetivos Específicos

- Realizar uma revisão sistemática dos artigos que avaliaram achados da TC de tórax em COVID-19 e de pneumonias virais de outra etiologia;
- Determinar a prevalência dos padrões de imagem (predominância opacidades vidro-fosco vs. consolidação) mais comum na TC de tórax de COVID-19 e outras pneumonias virais;
- Determinar a prevalência das características dos achados de imagem (bilateral vs. unilateral, periférico vs. central, etc.) em COVID-19 e outras pneumonias virais;
- Determinar a prevalência dos demais achados da TC de tórax (em COVID-19 e outras pneumonias virais.

# 7 MATERIAIS E MÉTODOS

## 7.1 Desenho do estudo

Revisão sistemática e meta-análise de estudos que avaliaram os achados tomográficos de pacientes imunocompetentes com COVID-19 e com outras pneumonias virais.

## 7.2 Critérios de elegibilidade

### *7.2.1 Critérios de inclusão*

- Infecção de trato respiratório confirmado por RT-PCR para algum dos seguintes vírus: SARS-CoV-2, adenovírus, influenza A H1N1, rinovírus, parainfluenza, vírus sincicial respiratório
- Idade ≥ 16 anos.
- Informação sobre os achados da TC de tórax.
- Casos de infecção aguda até 14 dias do início dos sintomas.

### *7.2.2 Critérios de exclusão*

- Relatos de caso com <10 pacientes.
- Estudos que incluíram pacientes imunocomprometidos ou que não separaram os imunocomprometidos da amostra total para análise estratificada.
- Ausência de informação em relação à idade dos pacientes e status imunocompetência.
- Outros vírus que não os descritos nos critérios de inclusão acima, que representam os patógenos mais prevalentes em pneumonias virais (REFs).
- Estudos não publicados em inglês.

## 7.3 Estratégia de revisão sistemática e extração de dados

O estudo será descrito conforme as orientações do *Preferred Reporting Items for Systematic Reviews* (PRISMA) e *Meta-Analysis of Observational Studies in Epidemiology* (MOOSE). A busca será realizada em todas as bases de literatura, incluindo PubMed-MEDLINE, EMBASE, e base de dados Cochrane até dia 04 de abril 2020. Será realizado uma pesquisa compreensiva com os seguintes termos para os

artigos de COVID-19: “COVID-19” ou “Coronavirus” ou “SARS-CoV-2”, “*imaging*” ou “*computed tomography*”. Para as outras pneumonias virais, será realizado a seguinte busca: “pneumonia”, “viral”, e “*imaging*” ou “*computed tomography*”.

Dois revisores independentes irão revisar todos os artigos individualmente para extração de dados. Os dados de cada revisor serão comparados e divergências serão resolvidas por consenso ou com a ajuda de um terceiro revisor com mais de 10 anos de experiência em radiologia torácica.

### 7.4 Variáveis de desfecho incluídas no estudo

Serão extraídos de cada estudo as seguintes informações na forma de prevalências: (1) Padrão tomográfico predominante (predominante vidro-fosco, predominante consolidação, misto, nenhum achado de imagem); (2) Características dos achados de imagem (e.g., predominantemente bilateral vs. unilateral, periférico vs. central, etc); (3) Lobos pulmonares envolvidos pelas alterações de imagem; (4) Outros achados tomográficos menos prevalentes.

### 7.5 Análise estatística

A análise de dados será realizada com software Stata versão 15.0 (StataCorp LP, College Station, Texas, USA). Será utilizado o comando “Metaprop” para o cálculo das prevalências combinadas para cada achado, além do intervalo de confiança de 95%. O índice $I^2$ será utilizado para quantificar a heterogeneidade entre os estudos. A análise será feita utilizando a modelo de efeitos randômicos dada a alta heterogeneidade esperada na combinação dos dados devido as diferenças de população e desenho dos estudos.

### 7.6. Orçamento e financiamento

Dada a natureza do estudo e seu desenho retrospectivo, não serão necessários recursos institucionais ou próprios para a execução do projeto. A análise será realizada pelo próprio autor e os arquivos serão armazenados de forma digital.

### 7.7 Aspectos éticos

Essa revisão sistemática e meta-análise não envolve pesquisa direta com seres humanos, portanto não há risco de exposição de dados de pacientes, já que foram utilizados apenas dados públicos não identificados.

### 7.8 Limitações do estudo

As limitações desse estudo incluem todas aquelas associadas à natureza do desenho do estudo (revisão sistemática) e aquelas associados à combinação dos dados (meta-análise). Essas limitações incluem, mas não são limitadas a: viés de seleção, viés de publicação, inclusão apenas de estudos em inglês, não inclusão de estudos que não tinham toda a informação necessária disponível, entre outras. Alta heterogeneidade é esperada na análise e também é um fator limitador, especialmente pois serão meta-analisados estudos de populações muito distintas (Ásia vs. América; H1N1 vs. adenovírus) e com diferenças subjetivas na mensuração das variáveis por cada autor.

## 8 RESULTADOS

Resultados do estudo submetidos e aceitos para publicação como artigo original na *European Radiology* (APÊNDICE I).

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# APÊNDICE I – Artigo original publicado na revista *European Radiology*

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COMPUTED TOMOGRAPHY

## Comparison of the computed tomography findings in COVID-19 and other viral pneumonia in immunocompetent adults: a systematic review and meta-analysis

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**Abstract**

**Objectives** To compare the chest computed tomography (CT) findings of coronavirus disease 2019 (COVID-19) to other non-COVID viral pneumonia.

**Methods** MEDLINE, EMBASE, and Cochrane databases were searched through April 04, 2020, for published English language studies. Studies were eligible if they included immunocompetent patients with up to 14 days of viral pneumonia. Subjects had a respiratory tract sample test positive for COVID-19, adenovirus, influenza A, rhinovirus, parainfluenza, or respiratory syncytial virus. We only included observational studies and case series with more than ten patients. The pooled prevalence of each chest CT pattern or finding was calculated with 95% confidence intervals (95% CI).

**Results** From 2263 studies identified, 33 were eligible for inclusion, with a total of 1911 patients (COVID-19, $n = 934$; non-COVID, $n = 977$). Frequent CT features for both COVID-19 and non-COVID viral pneumonia were a mixed pattern of ground-glass opacity (GGO) and consolidation (COVID-19, 0.37; 0.17–0.56; non-COVID, 0.46; 0.35–0.58) or predominantly GGO pattern (COVID-19, 0.42; 0.28–0.55; non-COVID 0.25; 0.17–0.32), bilateral distribution (COVID-19, 0.81; 0.77–0.85; non-COVID, 0.69; 0.54–0.84), and involvement of lower lobes (COVID-19, 0.88; 0.80–0.95; non-COVID, 0.61; 0.50–0.82). COVID-19 pneumonia presented a higher prevalence of peripheral distribution (COVID-19 0.77; 0.67–0.87; non-COVID 0.34; 0.18–0.49), and involvement of upper (COVID-19, 0.77; 0.65–0.88; non-COVID 0.18; 0.10–0.27) and middle lobes (COVID-19, 0.61; 0.47–0.76; non-COVID 0.24; 0.11–0.38).

**Conclusion** Except for a higher prevalence of peripheral distribution, involvement of upper and middle lobes, COVID-19, and non-COVID viral pneumonia had overlapping chest CT findings.

**Electronic supplementary material** The online version of this article (https://doi.org/10.1007/s00330-020-07018-x) contains supplementary material, which is available to authorized users.

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**Key Points**

- *Most common CT findings of coronavirus disease 2019 (COVID-19) were a predominant pattern of ground-glass opacity (GGO), followed by a mixed pattern of GGO and consolidation, bilateral disease, peripheral distribution, and lower lobe involvement.*
- *Most frequent CT findings of non-COVID viral pneumonia were a predominantly mixed pattern of GGO and consolidation, followed by a predominant pattern of GGO, bilateral disease, random or diffuse distribution, and lower lobe involvement.*
- *COVID-19 pneumonia presented a higher prevalence of peripheral distribution, and involvement of upper and middle lobes compared with non-COVID viral pneumonia*

**Keywords** Computed tomography · X-ray · Coronavirus · COVID-19 · Viral pneumonia

**Abbreviations**

| | |
|---|---|
| ACR | American College of Radiology |
| AdV | Adenovirus |
| COVID-19 | Coronavirus disease 2019 |
| CT | Chest tomography |
| EQUATOR | Enhancing the Quality and Transparency of Health Research |
| GGO | Ground-glass opacity |
| MOOSE | Meta-analysis Of Observational Studies in Epidemiology |
| PIV | Parainfluenza virus |
| PRISMA | Preferred Reporting Items for Systematic Reviews |
| RNV | Rhinovirus |
| RSV | Respiratory syncytial virus |
| RT-PCR | Reverse transcriptase polymerase chain reaction |

## Introduction

The emergence of the novel coronavirus 2019 disease (COVID-19) has caused an international outbreak of respiratory illness that ranges from mild, self-limited disease to severe pneumonia and death [1, 2]. The rapid spread of the virus outside China despite local and global attempts to restrain dissemination has garnered international attention, and the WHO declared this outbreak a global pandemic in early March 2020 [3]. Thus far, over one million cumulative cases have been reported worldwide, with a mortality rate of around five percent of cases [3].

Most patients present with fever, dry cough, and dyspnea in reported cohorts [4, 5]. Nearly 90% of hospitalized patients have abnormal findings on chest CT [5, 6], with bilateral ground-glass opacities (GGO) as one of the most common results reported on CT scans of patients with COVID-2019 [5, 6]. Other manifestations, such as consolidations, lower lobe predilection, and predominantly peripheral distribution of disease, are often reported in CT studies of patients with COVID-2019 [7–16]. In light of these common imaging manifestations, some authors have suggested considering chest CT as a primary tool for detection of COVID-2019 in epidemic areas as many patients have negative reverse transcriptase polymerase chain reaction (RT-PCR) for coronavirus on the initial presentation [6]. Nonetheless, these imaging findings are not specific to COVID-2019 and could be also be found in other viral pneumonia (e.g., influenza, adenovirus) and non-infectious diseases [17–39]. Furthermore, 6 to 25% of healthy asymptomatic patients can present GGO on chest CT scans, finding which has been described as one of the hallmarks of COVID-2019 [40, 41].

The aim of this manuscript was to perform a systematic review and meta-analysis of the chest CT findings of COVID-2019 and other viral pneumonia in immunocompetent adults to evaluate if any discriminatory imaging features may help to distinguish COVID-19 from other respiratory viruses.

## Methods

### Search strategy

This study was reported following Enhancing the Quality and Transparency of Health Research (EQUATOR) Reporting Guidelines, including the Preferred Reporting Items for Systematic Reviews (PRISMA) and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines. We searched all available literature published in the PubMed-MEDLINE, EMBASE, and Cochrane databases through April 04, 2020. The databases were comprehensibly searched using the terms "pneumonia," "viral," and "imaging" OR "computed tomography." Equivalent terms for each database and detailed search strategy are included in Supplementary File 1.

### Inclusion and exclusion criteria

Studies were eligible for inclusion if the following criteria were present: (1) subjects had a positive RT-PCR assay in a respiratory tract sample for one of the following viruses: 2019 avirus (2019-nCoV), adenovirus (AdV), influenza

A H1N1; rhinovirus (RNV); parainfluenza virus (PIV); respiratory syncytial virus (RSV); (2) report of chest computed tomography (CT) findings of viral pneumonia, including at least one of the following imaging features: predominant CT pattern or CT findings; (3) cases of acute infections up to 14 days of onset of symptoms; (4) immunocompetent patients ≥ 16 years; (5) design of the study as randomized and non-randomized controlled trials, observational studies, or case series.

To limit heterogeneity, we only included AdV, H1N1, RNV, RSV, and PIV as these were the most prevalent pathogens of viral pneumonia in immunocompetent hosts in previous studies [42–45]. We did not include other influenza A strains, such as H7N9, H5N1, H1N2, and H3N2.

Exclusion criteria were the following: (1) study population that included immunocompromised and did not stratify the analysis from immunocompetent patients; (2) lack of data regarding age and/or immunocompetency status; (3) case reports or series with less than ten subjects, letters to the editor, reviews, or meta-analysis; (4) studies not published in English; (5) studies with animals or in vitro.

### Data extraction

Two reviewers independently reviewed all included articles to extract data. Disagreements were solved by consensus or with the assistant of a third reviewer with more than 10 years of experience in thoracic radiology. Imaging features were defined following the Fleischner Society's glossary of terms in thoracic radiology [46].

From each study, we extracted the number of patients presenting the following imaging features: main CT pattern (predominantly or purely GGO; predominantly or purely consolidation; mixed GGO and consolidation; absence of GGO or consolidation), bilateral distribution; axial predominance (central; peripheral; random or diffuse); lobar predominance (upper lobes; middle lobes; lower lobes; random or diffuse (≥ 3 lobes).

Additionally, we also obtained the number of patients presenting the following chest CT findings: GGO, consolidation, nodules (tree-in-bud or centrilobular nodules), interstitial changes (interlobular septal thickening, reticulation, fibrosis), "crazy-paving" pattern, linear opacities, air bronchograms, bronchial wall thickening, vascular enlargement, reverse halo sign, pleural effusion, and mediastinal lymphadenopathy.

We only included data when studies described a per-patient report of the CT findings. As per-lesion analyses could be misleading, we considered the data as "not available" when the authors only described the absolute number of lesions, e.g., the number of GGO lesions. In studies which not all participating patients underwent a chest CT, we considered as the number of patients with a chest CT scan as the study sample size. When multiple publications including the same population was identified from an author group, we only included the most comprehensive study to avoid duplication of data.

### Study quality assessment

Two reviewers independently rated the quality of included studies using the National Institutes of Health Quality Assessment Tool for Case Series Studies [47]. Studies were not excluded due to their quality score to increase transparency and ensure all available evidence in this area was reported.

### Statistical analysis

All statistical analyses were performed using Stata version 15.0 (StataCorp LP). We used the Metaprop command to calculate the pooled prevalences of the included variables and their corresponding 95% confidence intervals (95% CI). The $I^2$ index was used to quantify the extent of heterogeneity. Due to limitations of the meta-analysis of variables with extreme proportions, i.e., zero (0%) or one (100%), the variable was added "n + 1" (in case of 0%) or subtracted "n-1" (in cases of 100%) when appropriate. Random-effects models were used as elevated levels of heterogeneity were expected due to differences in the population and methodology of the articles. We assessed the heterogeneity in main characteristics, including date of publication and study quality.

## Results

### Study characteristics

The initial search yielded 2263 studies, from which 96 were reviewed, and 33 met the inclusion criteria. A total of 10 studies on COVID-19 [7–16], and 23 studies on non-COVID viral pneumonias were included (Fig. 1) [17–39]. Although the article by Ng et al included a 10-year-old child, this patient had a normal chest CT and was removed from this analysis [13]. A total of 1911 patients were included, of which 934 (48.9%) were in the COVID group and 977 (51.1%) were in the non-COVID group. Summary findings of the studies included in this meta-analysis were presented in Tables 1 and 2. Methodologic quality was considered fair in all the included studies [7–39]. Publication bias was not able to be assessed due to the heterogeneity in the means of reporting data among different studies. In the non-COVID studies, H1N1 was the main pathogen in 19, AdV in 4, and in one study, there were multiple pathogens in the sample (AdV, H1N1, RSV, and PIV).

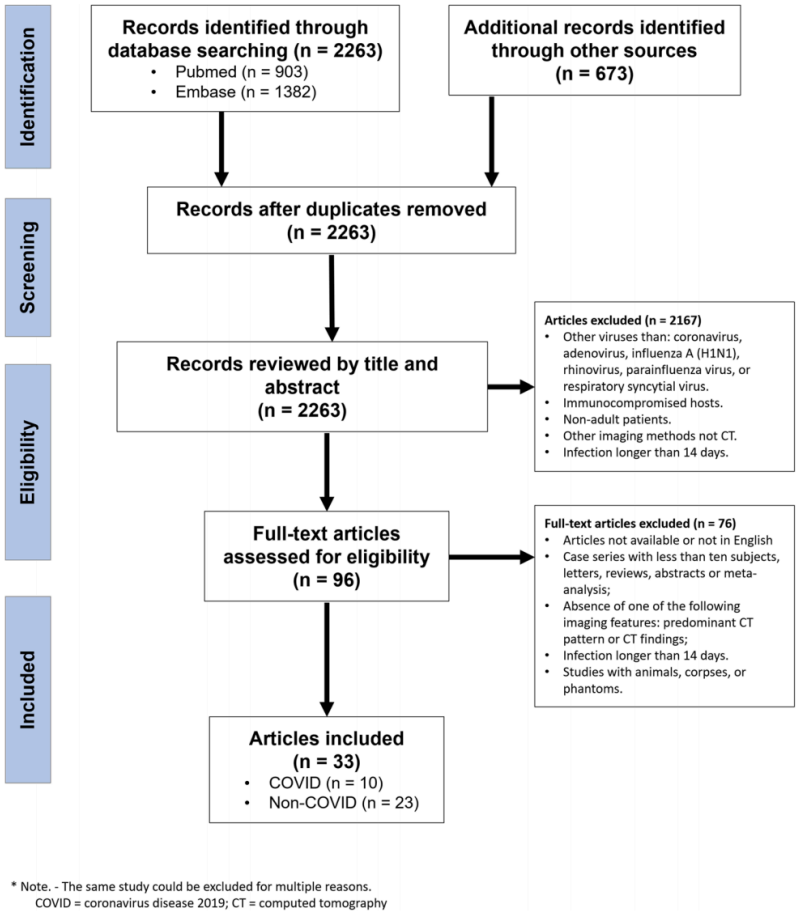


**Fig. 1** Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram

**Table 1** Main characteristics of COVID pneumonia studies ($n$ = 934 patients)

| Study | Pathogen | Sample size | Male, no. (%) | Age, mean, (SD) [IQR], years |
|---|---|---|---|---|
| Bai et al (2020), China | COVID-19 | 219 | 119 (54.3) | 44.8 (14.5) |
| Bernheim et al (2020), China | COVID-19 | 121 | 61 (50.4) | 45.3 (16) |
| Caruso et al (2020), Italy | COVID-19 | 158 | 83 (52.4) | 57 [18–80] |
| Inui et al (2020), Japan | COVID-19 | 112 | 59 (52.7) | 60 (17) |
| Li et al (2020), China | COVID-19 | 51 | 28 (54.9) | 58 [26–83] |
| Liu et al (2020), China | COVID-19 | 73 | 41 (56.2) | 41.6 (14.5) |
| Ng et al (2020), China | COVID-19 | 20 | 13 (61.9) | 56 [37–65] |
| Pan et al (2020), China | COVID-19 | 63 | 33 (52.4) | 44.9 (15.2) |
| Shi et al (2020), China | COVID-19 | 66 | 35 (53.0) | 49.5 (11) |
| Song et al (2020), China | COVID-19 | 51 | 25 (49.0) | 49 (16) |

*CI*, confidence intervals; *COVID*, coronavirus disease; *IQR*, interquartile range; *SD*, standard deviation

**Table 2** Main characteristics of non-COVID pneumonia studies ($n$ = 977 patients)

| Study | Pathogen | Sample size | Male, no. (%) | Age, mean, (SD) [IQR], years |
|---|---|---|---|---|
| Amorim et al (2013), Brazil | H1N1 | 71 | 33 (46.5) | 41.3 [16–92] |
| Cho et al (2011), South Korea | H1N1 | 37 | 21 (56.8) | 46.1 (17.3) |
| Grieser et al (2012), Germany | H1N1 | 23 | 16 (69.6) | 42.2 (16) |
| Henzler et al (2010), Germany | H1N1 | 10 | 6 (60.0) | 45.3 [27–65] |
| Hwang et al (2013), South Korea | AdV | 11 | 11 (100) | NA |
| Kang et al (2012), South Korea | H1N1 | 76 | 42 (55.3) | 52 [18–86] |
| Karadeli et al (2011), Turkey | H1N1 | 52 | 21 (40.4) | 41 (1.3) |
| Kim et al (2011), South Korea | H1N1 | 11 | NA | 30.7 [18–79] |
| Ishiguro et al (2016), Japan | H1N1 | 20 | 16 (80.0) | 59.9 (16.4) |
| Lee et al (2012), South Korea | H1N1 | 45 | 45 (100) | 20 [19–24] |
| Li et al (2011), China | H1N1 | 106 | 54 (50.9) | 31.7 (15.7) |
| Li et al (2011), China | H1N1 | 26 | 16 (61.5) | 53 [40–62] |
| Marchiori et al (2010), Brazil | H1N1 | 20 | 11 (55.0) | 42.7 [24–62] |
| Nicolini et al (2012), Italy | H1N1 | 28 | 15 (53.6) | 31.7 [26–78] |
| Park et al (2016), South Korea | AdV | 104 | 98 (94.2) | 20.1 [19–24] |
| Qi et al (2014), China | H1N1 | 16 | 0 | 27 [22–41] |
| Shiley et al (2010), USA | H1N1, AdV, RSV, PIV | 18 | 5 (27.8) | 55 |
| Sohn et al (2013), South Korea | H1N1 | 41 | 21 (51.2) | 46 [24–63] |
| Son et al (2011), South Korea | H1N1 | 20 | 13 (65.0) | 46.5 [18–69] |
| Song et al (2011), South Korea | H1N1 | 30 | 6 (20.0) | 36.6 (16.3) |
| Tanaka et al (2011), Japan | H1N1 | 10 | 6 (60.0) | 61.3 [26–85] |
| Valente et al (2011), Italy | H1N1 | 50 | NA | 40.9 [21–76] |
| Yoon et al (2017), South Korea | AdV | 152 | 152 (100) | 21 (2.1) |

*AdV*, adenovirus; *CI*, confidence intervals; *H1N1*, influenza A H1N1; *IQR*, interquartile range; *NA*, not available; *PIV*, parainfluenza virus; *RSV*, respiratory syncytial virus; *SD*, standard deviation

## Pooled prevalence of CT findings

Main CT features of COVID-19 and other viral pneumonia are summarized in Table 3. COVID-19 most commonly manifested with either a predominantly GGO pattern (0.42; 95% CI 0.28–0.55) (Fig. 2a), or a mixed pattern of GGO and consolidation (0.37; 95% CI 0.17–0.56) (Fig. 3a). Non-COVID viral pneumonia most often presented a mixed pattern of GGO and consolidation (0.46; 95% CI 0.35–0.58) (Fig. 3b) that was more commonly seen compared with a predominantly GGO pattern (0.25; 95% CI 0.17–0.32) (Fig. 2b). The predominant consolidation pattern was the least common of both groups (COVID-19, 0.04; 95% CI 0.01–0.07; vs non-COVID, 0.17; 95% CI 0.11–0.23) (Fig. 4). Heterogeneity was high and significant for all analyses on predominant CT patterns in both groups.

In both COVID-19 and non-COVID viral pneumonia, chest CT findings were bilateral (COVID-19, 0.81; 95% CI 0.77–0.85; non-COVID, 0.69; 0.54–0.84) (Supplementary Fig. 1) and most often involved the lower lobes (COVID-19, 0.88; 95% CI 0.80–0.95; non-COVID, 0.61; 0.44–0.78) (Supplementary Fig. 2). However, COVID-19 pneumonia presented a higher prevalence of peripheral distribution (COVID-19, 0.77; 95% CI 0.67–0.87; non-COVID, 0.34; 95% CI 0.18–0.49) (Supplementary Fig. 3), and involvement of upper lobes (COVID-19, 0.77; 95% CI 0.65–0.88; non-COVID, 0.18; 95% CI 0.10–0.27) (Supplementary Fig. 4) and middle lobe (COVID-19, 0.61; 95% CI 0.47–0.76; non-COVID, 0.24; 95% CI 0.11–0.38) (Supplementary Fig. 5). The most prevalent axial distribution of lesions in non-COVID was a diffuse or random distribution (0.50; 95% CI 0.35–0.65).

GGO was the most common CT finding, found in up to 0.92 (95% CI, 0.90–0.97) of COVID-19 and 0.80 (95% CI, 0.74–0.85) of non-COVID (Supplementary Fig. 6), followed by consolidation (COVID-19, 0.50; 95% CI 0.33–0.66; non-COVID, 0.69, 95% CI 0.61–0.77) (Supplementary Fig. 7). Pleural effusion was rare in COVID-19 (0.03; 95% CI 0.01–0.04), but more common in other viral pneumonia (0.25; 95% CI 0.18–0.32) (Supplementary Fig. 8). A case of COVID-19 presenting the most prevalent CT findings is shown in Fig. 5. We also present a patient diagnosed with H1N1 and typical images features of COVID-19 (Fig. 6).

## Discussion

The most prevalent chest CT findings in patients with COVID-19 were a predominantly GGO pattern (0.42;

**Table 3** Main CT features of COVID-19 pneumonia compared with other viral pneumonia

| Imaging features | COVID-19<br>Pooled prevalence (95% CI) | Non-COVID<br>Pooled prevalence (95% CI) |
|---|---|---|
| Predominant CT pattern | | |
| Predominantly GGO | 0.42 (0.28–0.55) | 0.25 (0.17–0.32) |
| Predominantly consolidation | 0.04 (0.01–0.07) | 0.17 (0.11–0.23) |
| Mixed GGO and consolidation | 0.37 (0.17–0.56) | 0.46 (0.35–0.58) |
| Absence of GGO or consolidation | 0.09 (0.04–0.14) | 0.05 (0.03–0.07) |
| Location | | |
| Bilateral | 0.81 (0.77–0.85) | 0.69 (0.54–0.84) |
| Axial distribution | | |
| Peripheral | 0.77 (0.67–0.87) | 0.34 (0.18–0.49) |
| Random or diffuse | 0.21 (0.09–0.34) | 0.50 (0.35–0.65) |
| Lobe involvement (craniocaudal) | | |
| Upper lobes | 0.77 (0.65–0.88) | 0.18 (0.10–0.27) |
| Middle lobes | 0.61 (0.47–0.76) | 0.24 (0.11–0.38) |
| Lower lobes | 0.88 (0.80–0.95) | 0.61 (0.44–0.78) |
| Findings | | |
| GGO | 0.92 (0.89–0.96) | 0.80 (0.74–0.85) |
| Consolidation | 0.47 (0.32–0.63) | 0.69 (0.61–0.77) |
| Nodules | 0.14 (0.04–0.24) | 0.30 (0.19–0.40) |
| Interstitial changes* | 0.27 (0.11–0.43) | 0.27 (0.19–0.35) |
| Pleural effusion | 0.03 (0.01–0.04) | 0.25 (0.18–0.32) |

*CI*, confidence intervals; *COVID*, coronavirus disease; *CT*, computed tomography; *GGO*, ground-glass opacity

*Interlobular septal thickening, reticulation, fibrosis

95% CI 0.28–0·55), followed by a mixed pattern of GGO and consolidation (0.37; 95% CI 0.17–0.56), bilateral disease (0.81; 95% CI 0.77–0.85), and involvement of the lower lobes (0.88; 95% CI 0.80–0.95). The most prevalent findings in non-COVID viral pneumonia were a mixed pattern of GGO and consolidation (0.49; 95% CI 0.39–0.62), followed by a predominantly GGO pattern (0.25; 95% CI 0.17–0.32), bilateral disease (0.69; 95% CI 0.53–0.85), and involvement of the lower lobes (0.61; 95% CI 0.44–0.78). Compared with other viral pneumonia, COVID-19 demonstrated a higher prevalence of peripheral distribution (0.77; 95% CI 0.67–0.87), and involvement of upper (0.77; 95% CI 0.65–0.88) and middle lobes (0.61; 95% CI 0.47–0.76).

The prevalence of upper and middle zone disease observed in the non-COVID population is likely underestimated. Many authors in this group used the terms "random zone predominance" or "diffuse involvement" referring to patients with involvement of multiple or all lobes, instead of describing which individual lobes were affected [17, 18, 23, 34]. Thus, patients in these two categories were not included in the analysis of individual lobar distribution, even though some of them possibly had upper and middle zone involvement. All the COVID-19 studies individually described which lobes were affected in their population.

The use of chest CT scan as a primary tool for screening of patients under investigation for COVID-19 is fraught with significant issues [48, 49]. This approach will result in an increased number of CTs in stable patients that otherwise would not be scanned, leading to increased costs and reduced access to imaging suites, as the entire room would have to be extensively sanitized after every case with suspicion for COVID-19 [49, 50]. Moreover, the CT scanner may act as a fomite of COVID-19 transmission. Therefore, the American College of Radiology (ACR) urges caution on such approach as a standard CT (especially in the early phases of COVID-19) should not dissuade a patient from viral testing, quarantine, and appropriate treatment [51]. Also, an abnormal CT should not be seen as diagnostic, as the same pattern may be seen in other viral pneumonia, as demonstrated in this study. Such resemblance should be acknowledged as the COVID-19 emerged simultaneously to the current seasonal influenza in the Northern Hemisphere.

There are two systematic reviews on CT findings on COVID-19 available in the literature with similar results to our study regarding the most common imaging findings in COVID-19 [52, 53]. Nonetheless, our review differs from those two by not including case series of less than 10 patients, population with pediatric or immunocompromised patients,

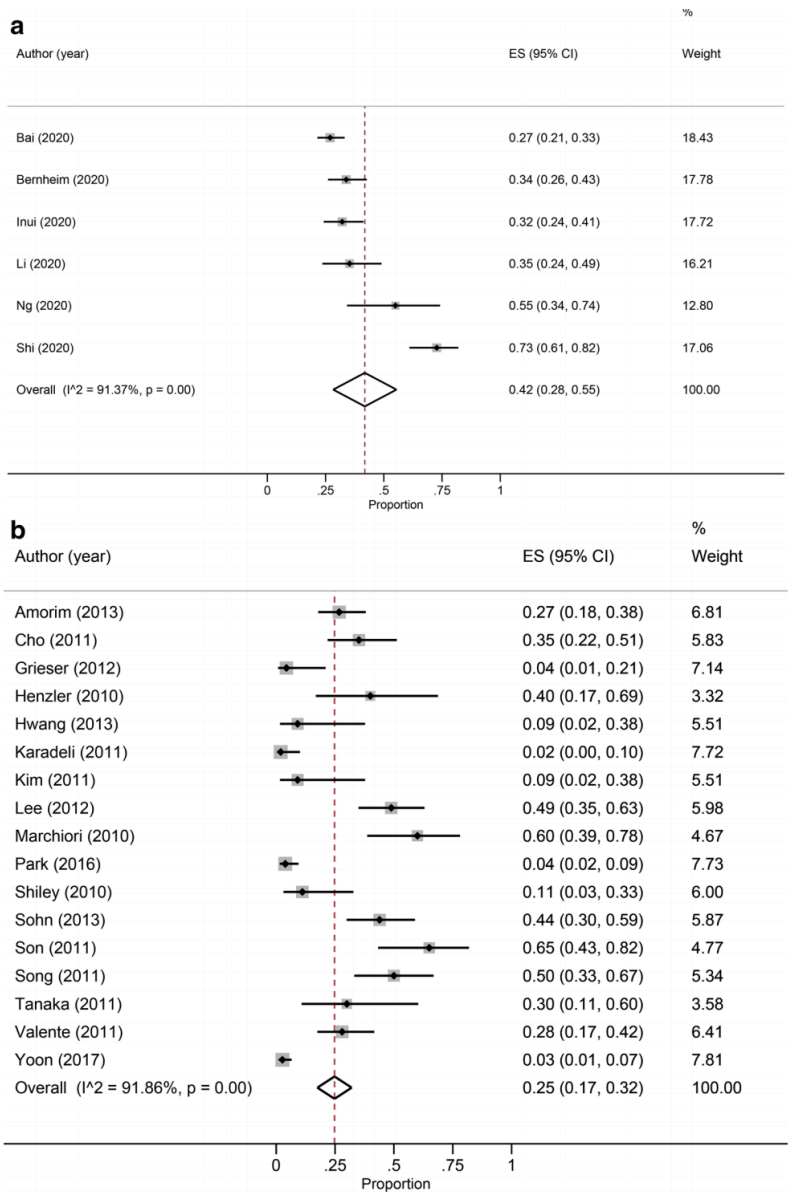


**Fig. 2** Forest plot of the pooled prevalence of "predominantly or purely ground-glass opacity" as the main CT pattern in COVID-19 (**a**) and non-COVID (**b**) studies. This was the most common predominant pattern in patients with COVID-19, and the second most prevalent pattern in non-COVID viral pneumonia. Heterogeneity was high and significant for both COVID-19 and non-COVID studies

and studies in which a percentage of the population did not have the diagnosis of COVID-19 confirmed by PCR, such as Ai et al [6]. We still had high heterogeneity between studies, which could be attributed to several factors. First, chest CT features, such as the predominant imaging pattern, depending on the time course of the infection when the patient is scanned [8, 14, 54]. A predominant pattern of GGOs is expected in the early course of COVID-19, whereas a mixed pattern often peaks between the second and third week of infection [54]. To limit this temporal variation of findings, we only included cases of acute infection with up to 14 days of evolution. Another possible cause of inter-study heterogeneity was a non-standard description of the CT findings throughout the studies, which lead to a significant number of

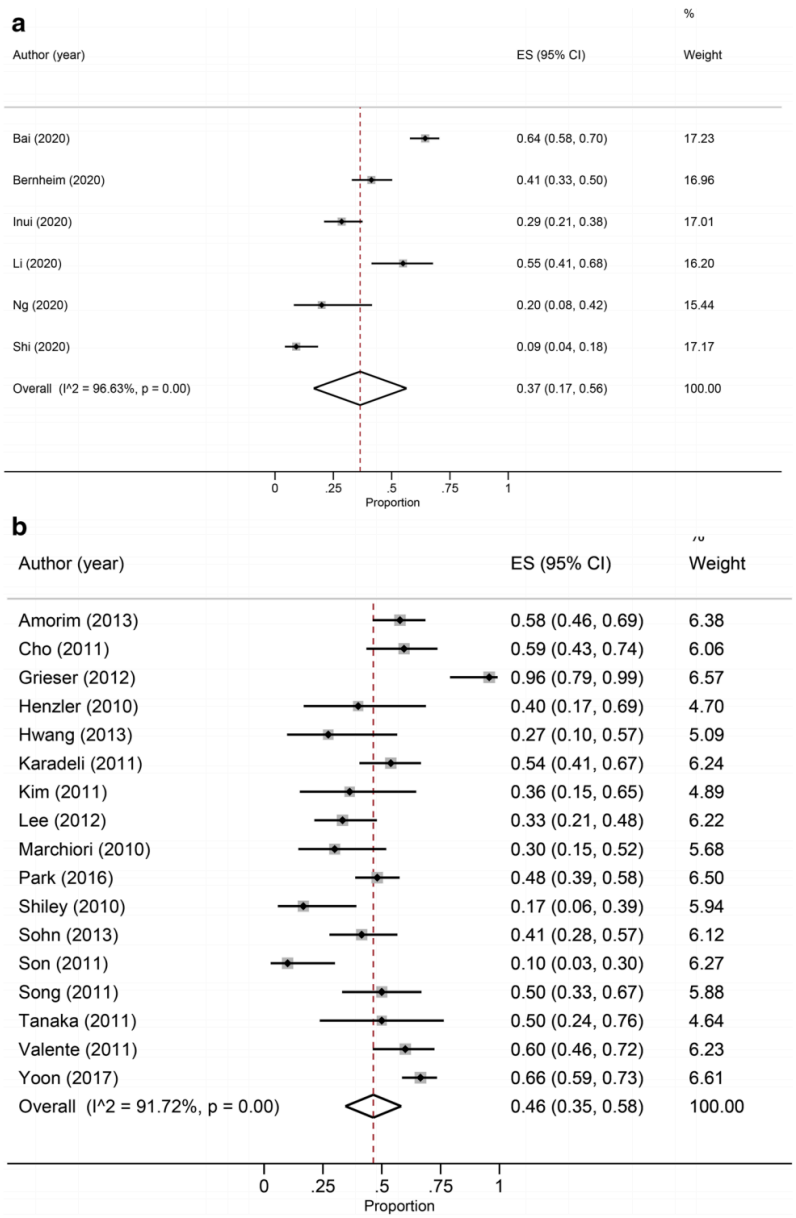


**Fig. 3** Forest plot of the pooled prevalence of "mixed ground-glass opacity and consolidation" as the main CT pattern in COVID-19 (**a**) and non-COVID (**b**) studies. This was the most prevalent CT pattern in non-COVID viral pneumonia. Heterogeneity was high and significant for both groups

missing data. By including only immunocompetent patients, we tried to reduce such heterogeneity of CT findings. Differences in CT scanners and protocols can also be accounted for the high inter-study heterogeneity. Also, the higher prevalence of pleural effusion in non-COVID studies, especially in the studies by Henzler et al and Grieser et al, could be attributed to pulmonary congestion of critically ill patients rather than a common manifestation of viral pneumonia [29, 32].

Several studies herein discussed have attempted to determine the diagnostic accuracy of chest CT to diagnose COVID-19. However, many are at risk of bias due to

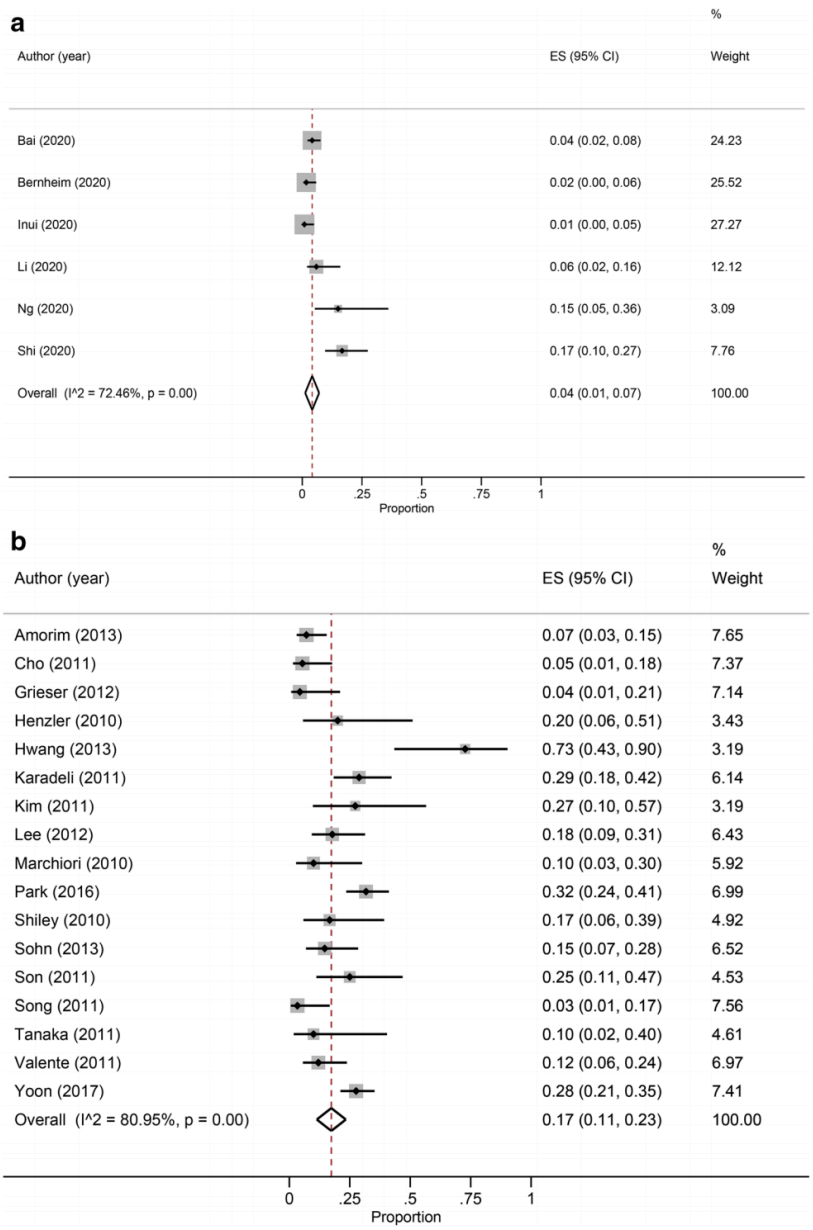


**Fig. 4** Forest plot of the pooled prevalence of "predominantly or purely consolidation" as the main CT pattern in COVID-19 (**a**) and non-COVID (**b**) studies. This was the least common CT pattern for both COVID-19 and non-COVID patients. Heterogeneity was high and significant for both COVID-19 and non-COVID studies

methodology limitations, such as lack of a control population and questionable reference tests. As a result, CT estimates of sensitivity and specificity could be flawed [55]. For instance, Ai et al reported a sensitivity of 97% and suggested chest CT as a primary tool for the detection of COVID-19 in epidemic areas [6]. Bai et al also found that CT was abnormal in more than 90% of RT-PCR confirmed cases of COVID-19 [7]. On the other hand, Inui and colleagues described that only 61% of positive cases from Diamond Princess cruise ship had lung opacities on chest CT [10]. We believe the statistics of the latter comes closer to what would be expected in the general population, especially considering patients who are not very symptomatic and undergo chest CT scanning.

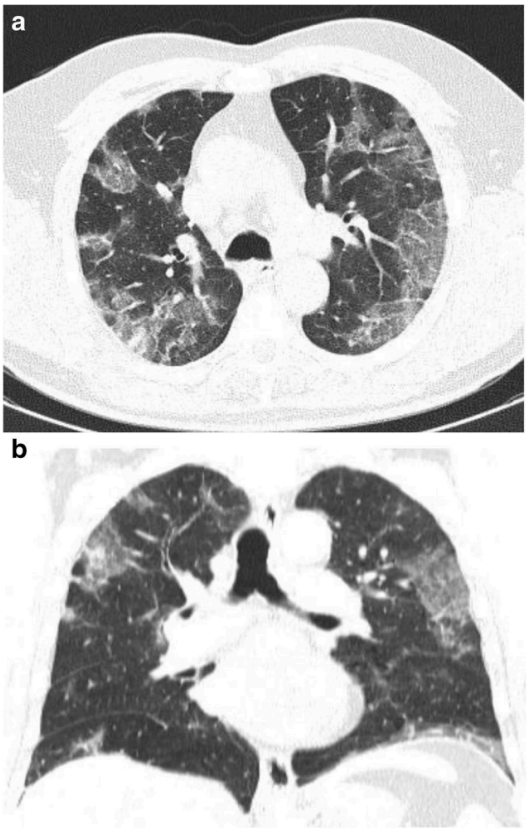


**Fig. 5** 60-year-old man presenting with typical CT findings of COVID-19 confirmed by RT-PCR. **a** Axial chest CT demonstrates bilateral subpleural ground-glass opacities with superimposed smooth interlobular septal thickening (crazy-paving). **b** Coronal reformatted CT shows bilateral upper to mid lung gradient, though the lower lobes were involved to a lesser extent

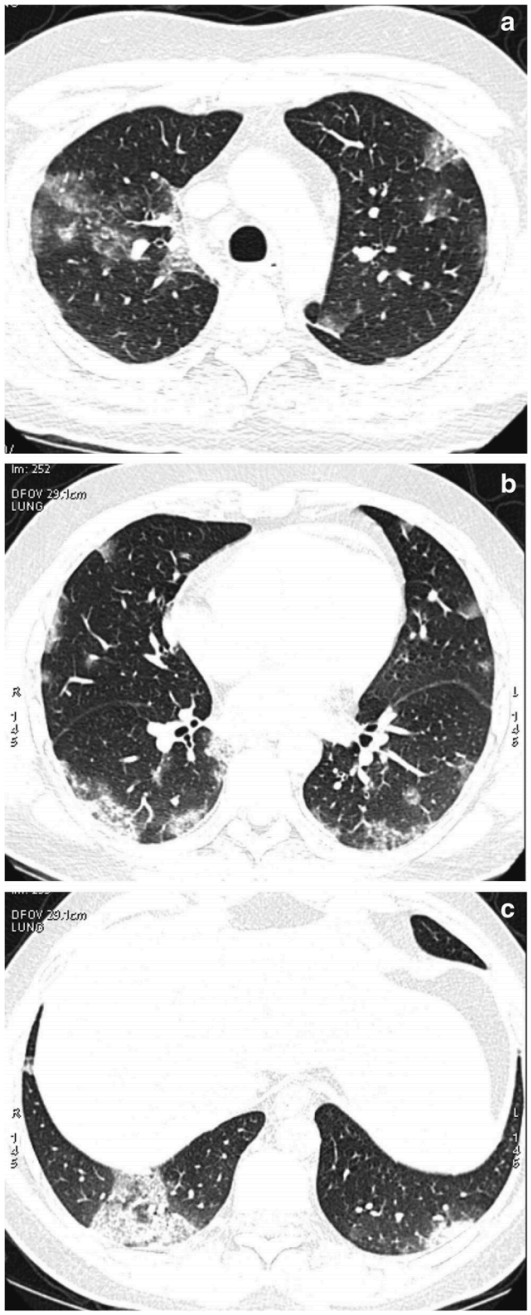


**Fig. 6** 31-year-old man with a diagnosis of H1N1. **a**, **b**, **c** Axial chest CT shows multiple subpleural ground-glass opacities and consolidations bilaterally

Bai et al investigated the performance of radiologists in differentiating COVID-19 from other viral pneumonia [7]. The authors found that American radiologists had a surprisingly high accuracy in distinguishing COVID-19 from other viral pneumonia. However, the reproducibility of these findings is questionable, as authors considered as references in the control group patients that had word "pneumonia" in their radiology CT reports and a positive result from respiratory pathogen panel. Also, bilateral GGOs have a much broader differential, present in atypical infections, non-infectious processes, and even in healthy individuals [40, 41]. Also, some patients with COVID-19 pneumonia may have a normal chest CT scan [50].

This study has some limitations. First, there were limitations common to any meta-analyses of diagnostic tests (e.g., selection bias, publication bias, missing information). Virtually all studies herein included had a retrospective

design, which is also a limitation. The exclusion of studies not available in English could have increased the probability of publication bias. Regarding selection bias, the etiological agents of non-COVID studies were not entirely comprehensible for all viruses associated with community-acquired viral pneumonia (e.g., rhinovirus). Few studies using chest CT in immunocompetent adults are available, as CT imaging is considered "usually not appropriate" by the ACR in this scenario [51]. Also, the heterogeneity in the results was high due to the reasons discussed above. Finally, the methodology for measuring variables (e.g., axial distribution, predominant CT pattern) was not standardized among manuscripts.

## Conclusion

Except for a higher prevalence of peripheral distribution, involvement of upper and middle lobes, COVID-19, and non-COVID viral pneumonia has overlapping chest CT findings. As such, caution should be exercised when interpreting chest CT for COVID-19 and the use of this imaging modality as a first-line test for COVID-19 diagnosis.

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### Compliance with ethical standards

**Guarantor** The scientific guarantor of this publication is Bruno Hochhegger, MD, PhD.

**Conflict of interest** The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article.

**Statistics and biometry** One of the authors has significant statistical expertise.

**Informed consent** Not applicable since this was a systematic review and did not include information on human subjects.

**Ethical approval** Not applicable since this was a systematic review and did not include information on human subjects.

**Methodology**
• Systematic review and meta-analysis

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## ANEXO I – Aprovação da comissão científica da Escola de Medicina da Pontifícia Universidade Católica do Rio Grande do Sul

S I P E S Q

Sistema de Pesquisas da PUCRS

Código SIPESQ: 10113 Porto Alegre, 26 de abril de 2021.

Prezado(a) Pesquisador(a),

A Comissão Científica da ESCOLA DE MEDICINA da PUCRS apreciou e aprovou o Projeto de Pesquisa "AVALIAÇÃO DOS ACHADOS DE TOMOGRAFIA COMPUTADORIZADA EM PACIENTES IMUNOCOMPETENTES COM COVID-19 COMPARADO A OUTRAS PNEUMONIAS VIRAIS: REVISÃO SISTEMÁTICA E META-ANÁLISE", previamente aprovado por esta Comissão em 09/11/2020.

Atenciosamente,

Comissão Científica da ESCOLA DE MEDICINA