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Detection of subsolid nodules on chest CT scans during the COVID-19 pandemic

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ABSTRACT

Objective: To investigate the detection of subsolid nodules (SSNs) on chest CT scans of outpatients before and during the COVID-19 pandemic, as well as to correlate the imaging findings with epidemiological data. We hypothesized that (pre)malignant nonsolid nodules were underdiagnosed during the COVID-19 pandemic because of an overlap of imaging findings between SSNs and COVID-19 pneumonia. **Methods:** This was a retrospective study including all chest CT scans performed in adult outpatients (> 18 years of age) in September of 2019 (i.e., before the COVID-19 pandemic) and in September of 2020 (i.e., during the COVID-19 pandemic). The images were reviewed by a thoracic radiologist, and epidemiological data were collected from patient-filled questionnaires and clinical referrals. Regression models were used in order to control for confounding factors. **Results:** A total of 650 and 760 chest CT scans were reviewed for the 2019 and 2020 samples, respectively. SSNs were found in 10.6% of the patients in the 2019 sample and in 7.9% of those in the 2020 sample ($p = 0.10$). Multiple SSNs were found in 23 and 11 of the patients in the 2019 and 2020 samples, respectively. Women constituted the majority of the study population. The mean age was 62.8 ± 14.8 years in the 2019 sample and 59.5 ± 15.1 years in the 2020 sample ($p < 0.01$). COVID-19 accounted for 24% of all referrals for CT examination in 2020. **Conclusions:** Fewer SSNs were detected on chest CT scans of outpatients during the COVID-19 pandemic than before the pandemic, although the difference was not significant. In addition to COVID-19, the major difference between the 2019 and 2020 samples was the younger age in the 2020 sample. We can assume that fewer SSNs will be detected in a population with a higher proportion of COVID-19 suspicion or diagnosis.

Keywords: Solitary pulmonary nodule; Multiple pulmonary nodules; Lung neoplasms/diagnostic imaging; Tomography, X-ray computed; COVID-19.

INTRODUCTION

Subsolid nodules (SSNs) are common findings in chest CT scans and represent a subset of pulmonary nodules that may have proliferative potential and should be monitored when persistent. They include ground-glass nodules (GGNs) and part-solid nodules (PSNs).[1,2]

In a study of CT screening for lung cancer,[3] persistent SSNs accounted for 19% of all positive results, the malignancy rate being higher for SSNs than for solid nodules of the same size.

In recent years, there has been an increase in the detection of all types of lung nodules as a result of the widespread availability of CT scanners, advances in CT technology, positive results of lung cancer screening programs,[4,5] and increased CT utilization in clinical practice.[6]

Chest CT is a fast, noninvasive method for evaluating respiratory diseases, widely used for the evaluation of pneumonia during the COVID-19 pandemic.[7] Because numerous imaging findings have been reported in association with COVID-19, the Radiological Society of North America published in March of 2020 an expert consensus document stating that COVID-19 pneumonia typically presents with multifocal, rounded ground-glass opacities with or without consolidation and septal thickening.[8]

The objective of the present study was to investigate whether the overlap of imaging findings between SSNs and COVID-19[9] could affect the detection of GGNs and PSNs on chest CT scans.

METHODS

This was a retrospective study including all chest CT scans performed in September of 2019 and in September of 2020 in the radiology department of a tertiary care hospital in southern Brazil. The study was approved by the institutional review board of the hospital (Protocol no. 4.260.736, September 5, 2020), and the requirement for

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written informed consent was waived because of the noninterventional, retrospective nature of the study.

Inclusion criteria were being > 18 years of age and having undergone CT in accordance with a standardized chest CT protocol; exclusion criteria were being < 18 years of age and having undergone CT in accordance with other protocols (e.g., cardiac CT and radiation therapy planning scans). Emergency room patients and inpatients were not included in the evaluation, in order to avoid nosocomial pneumonia and other hospital-acquired complications that could add confounding factors to the study.

All CT images were reviewed by a thoracic radiologist who had 10 years of experience and who had access to the epidemiological data, which were collected from patient-filled questionnaires and clinical referrals. All chest CT scans were obtained with a 16-slice or a 256-slice multidetector scanner (SOMATOM Emotion 16; Siemens Healthineers, Forcheim, Germany and SOMATOM Drive 256; Siemens Healthineers, respectively) at end inspiration, with or without contrast enhancement, with the patients in the supine position. Although most of the CT examinations were standard-dose HRCT scans of the chest, some were contrast-enhanced CT scans, low-dose CT scans, or CT pulmonary angiography scans. Image data sets were reconstructed with 1-mm slice thickness and increments of 0.7 mm and 0.5 mm, with the use of soft-tissue and sharp kernels and standard lung window settings.

All CT images were evaluated for SSNs and their features, including number, size, density (pure GGNs, heterogeneous GGNs, and PSNs), lobar distribution, and number of affected lobes. All nodules were measured at their longest and shortest axes, the lung window being used for the ground-glass component. The solid component was measured when detected in the soft-tissue window. Multiple nodules were included. Subsequently, all CT images were evaluated for the presence and quantification of emphysema with the use of a visual scale.[10]

COVID-19 patients were defined as those referred for CT examination as COVID-19 patients (i.e., not necessarily presenting with a positive RT-PCR result). All other patients were considered non-COVID-19 patients. Although this was an arbitrary choice, our decision was based on the idea that suspicion of SARS-CoV-2 infection can interfere with the interpretation of CT images even without laboratory confirmation. In addition, we chose not to blind the radiologist who evaluated the CT images. Therefore, for COVID-19 patients, CT scans were read as positive for SSNs when lesions were not typical for COVID-19 in accordance with the Radiological Society of North America expert consensus document, including solitary nodules and persistent nodules in patients who had previously undergone imaging. Multiple nodules were not considered positive for SSNs, except in patients who had previously undergone imaging tests, which were reviewed when available, in accordance with best practice recommendations. For non-COVID-19 patients, CT scans were read as positive for SSNs if one or more (persistent or new) GGNs or PSNs were found. For COVID-19 patients, we reviewed all follow-up CT scans available by February of 2022.

Statistical analysis was performed with R software, version 4.2.3 (R Foundation for Statistical Computing, Vienna, Austria). Categorical variables are shown as absolute numbers (n) or relative frequencies (%). Continuous variables such as age are shown as mean ± SD. The Shapiro-Wilk test was used in order to verify the normal distribution of variables. Nonparametric data were analyzed with the Mann-Whitney Wilcoxon test and the chi-square test, with a 0.05 significance level. Poisson regression with robust variance was used for regression models.

RESULTS

The baseline characteristics of the patients and a flow chart of the study are shown in Table 1 and Figure 1, respectively.

The number of CT scans was 17% higher in September of 2020 than in September of 2019. At that moment in 2020, Brazil was experiencing a transition between the end of the first and the beginning of the second wave of the COVID-19 pandemic.[11]

Females constituted the majority of the study population. No significant differences were found between the September of 2019 and September of 2020 samples regarding sex ($p = 0.07$). The mean age was 62.8 ± 14.8 years in the 2019 sample and 59.5 ± 15.1 years in the 2020 sample ($p < 0.01$).

The proportion of patients with a history of cancer was 45.7% in 2020 and 50.7% in 2019 ($p = 0.07$). Cancer types included breast, gastrointestinal, rectal, prostate, melanoma, head and neck, and lung, as well as lymphoproliferative disorders, in initial staging or follow-up. Metastatic lung disease was present in 5.1% and 4.6% of the oncologic patients, respectively.

Current smokers and former smokers within 15 years of quitting constituted 24.1% of the 2019 sample and 21.1% of the 2020 sample ($p = 0.3$). Emphysema was found in 22.5% of the patients in the 2019 sample and in 19.7% of those in the 2020 sample.

SSNs were found in 10.6% of the patients in the 2019 sample and in 7.9% of those in the 2020 sample ($p = 0.10$). The detection rates for 2019 and 2020 were 1.34 and 1.23, respectively (95% CI, 0.96-1.86; $p = 0.084$). After Poisson regression with robust variance for age and sex, the difference remained nonsignificant (95% CI, 0.89-1.71; $p = 0.215$).

SSN-positive patients in the 2019 sample (mean age, 66.8 ± 13.3 years) were significantly older than SSN-negative patients ($p = 0,015$). This difference was not significant for the patients in the 2020 sample, although SSN-positive patients were older than SSN-negative patients (61.8 ± 13.7 years; $p = 0.186$).

Table 1. Baseline characteristics of the patients included in the study.

Characteristic		September of 2019	September of 2020	p	COVID-19 September of 2020
Valid exams, n		650	760	-	175
Female sex, %		58.2%	53.6%	0.07	52.8%
Age, years (mean ± SD)		62.8 ± 14.8	59.5 ± 15.1	< 0.01	53.2 ± 13.5
History of cancer		50.7%	45.7%	0.07	-
Current smokers or former smokers within 15 years of quitting, %		24.1%	21.1%	0.3	-
Emphysema	No	77.5%	80.1%		
	Mild	14.3%	14.0%		
	Moderate to severe	8.2%	5.7%		

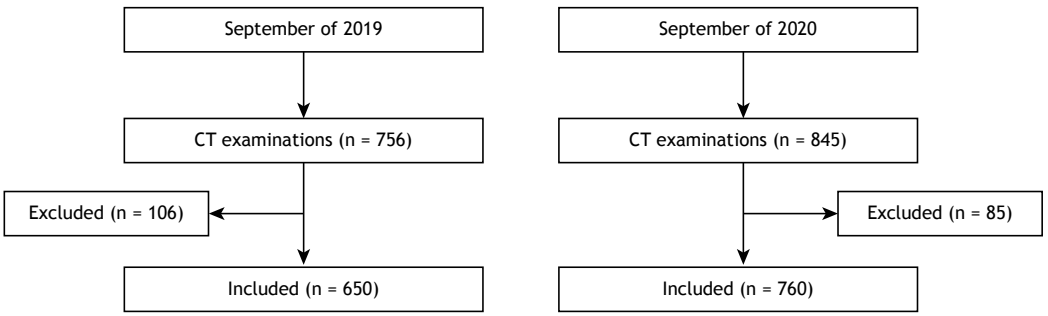

Figure 1. Flow chart of the study.

Multiple SSNs were found in 23 patients in the 2019 sample and in 11 patients in the 2020 sample (10 non-COVID-19 patients and 1 COVID-19 patient with two persistent GGNs).

COVID-19 patients constituted 24% of the 2020 sample (females, 52.8%; mean age, 53.2 ± 13.5 years). If we take into consideration that COVID-19 cases in southern Brazil were first reported in March of 2020, the maximum time interval between infection with SARS-CoV-2 and data collection was 6 months. SSNs were detected in 6.7% of COVID-19 patients (n = 12; solitary nodules, in 11; females, 58%). Of those 12 patients, 8 showed persistent SSNs on subsequent CT scans (resected adenocarcinoma, in 1; Figure 2), 3 did not undergo follow-up imaging, and 1 had a solitary GGN that disappeared within 6 months. Follow-up CT scans were available for 98 of 175 COVID-19 patients.

Non-COVID-19 patients constituted 76% of the 2020 sample, SSNs being detected in 9.3%. Using regression models for age and sex in order to compare SSN-positive patients between the 2020 COVID-19 subpopulation and the 2019 sample, we found a detection rate of 0.79 (95% CI, 0.43-1.44; p = 0.44) for COVID-19 patients. SSNs were more commonly detected in women, independently of the COVID-19 status (p = 0.006), as well as in older patients (p = 0.010). Table 2 shows the characteristics of the SSN-positive subgroups in the 2019 and 2020 samples.

DISCUSSION

SSNs are a cause for concern when persistent, because of their cancer potential.[1-3] However, there is a highly variable rate of inflammatory lesions first detected as SSNs on imaging.

As thoracic radiologists, we experienced reasonable diagnostic uncertainty when reading chest CT scans during the COVID-19 pandemic, especially when ground-glass lesions were few, nonperipheral, or even part solid, because of the overlap between ground-glass lesions and consolidation. Although most lesions were probably inflammatory given the clinical context, some (pre) malignant subsolid lesions could have been missed.

To overview these imaging limitations, our study sought to evaluate SSN detection before and during the COVID-19 pandemic. We chose to investigate outpatients in order to avoid inpatient complications. We chose the month of September because the lockdown in Brazil was over by then, with outpatient visits and tests being partially resumed at the beginning of the second wave of the pandemic.

In our study, almost a quarter of the patients undergoing chest CT as outpatients in September of 2020 had been referred to us as COVID-19 patients. The number of SSNs detected in the 2020 sample was lower than that of SSNs detected in the pre-pandemic (2019) sample, especially in the COVID-19 subpopulation, including multiple lesions. Nevertheless, the difference was not significant.

A confounding factor to consider is that the mean age was lower in the 2020 sample. This could lead us to conclude that we found fewer SSNs because of the younger age in the 2020 sample. However, it is debatable whether that age difference has actual

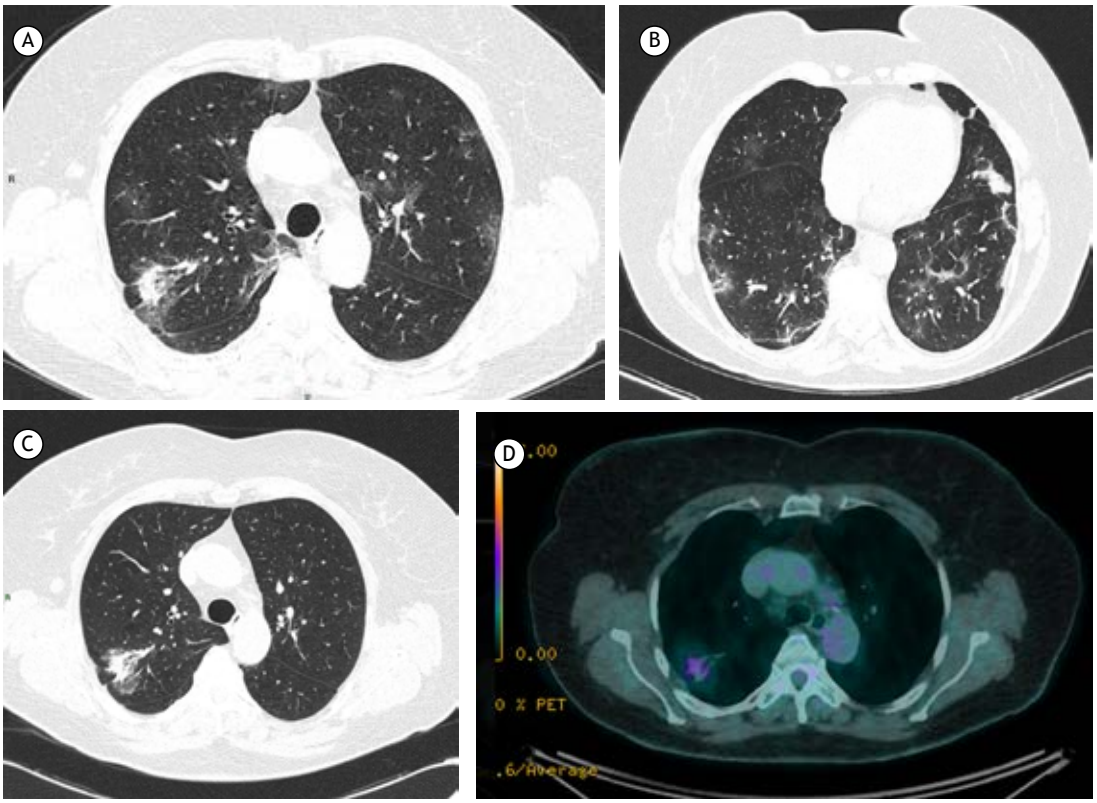

Figure 2. Chest CT scans. In A and B, part-solid nodule in the right upper lobe, as seen on the initial CT scan of a COVID-19 patient with pneumonia and other ground-glass and consolidative opacities. In C and D, part-solid nodule in the right upper lobe, as seen on the follow-up CT scan after regression of viral inflammatory lesions (in C), as well as FDG uptake on PET-CT scans (resected adenocarcinoma; in D).

Table 2. Detection of subsolid nodules before and during the COVID-19 pandemic.

Detection of SSNs	September of 2019	September of 2020	p	COVID-19
SSN, % (n/N)	10.6% (69/650)	7.9% (60/760)	0.10	6.7% (12/175)
Age, years (mean ± SD)	69 ± 13.3*	61.8 ± 13.7**	-	-
Female sex, %	73.9%	71.7%		58%
Symptoms†	36.2%	35%	0.9	
Solitary SSN	67%	72%	-	(11/12)
Multiple SSNs	33%	18%	-	(1/12)
Size < 20 mm[a]	95%	92%		
Upper lobes[b]	63.7%	60%	-	-

SSN: subsolid nodule; and COVID-19: patients referred for CT examination as COVID-19 patients (i.e., not necessarily presenting with a positive RT-PCR result). *p = 0.015. **p = 0.186. †Fever, dyspnea, cough, or any combination of the three. [a]Longest diameter of the nodule. [b]The most suspicious lesion was located in the upper lobes, in accordance with imaging criteria.

clinical significance, because it is known that SSNs tend to grow slowly or even remain stable for years. It is also of note that solitary and multiple SSNs are known to be potential (pre) malignant lesions, and previous studies have shown that up to 18% of resected adenocarcinomas are multiple.[12]

Women constituted the majority in our study and predominated in the SSN-positive subgroups. The detection of SSNs in women is a cause for concern, given that lung cancer screening studies have found that women are at a higher risk of cancer in a nonsolid nodule.[13] In addition, there has been an increasing frequency of lung cancer in nonsmokers.[14]

In our study, patients in the SSN-positive subgroups were older than the others in the 2019 and 2020 samples. The association between increasing age and persistent SSNs has been reported elsewhere.[13,15]

Of the 12 patients who were positive for SSNs in the COVID-19 subgroup, 1 had a PSN that turned out to be a lung adenocarcinoma. The nodule raised

suspicion at follow-up imaging only, having raised no suspicion during acute viral pneumonia. There are similar reports in the literature on lung cancer and concurrent pneumonia,[16,17] and one study conducted in China showed that lung cancer was the most common type of cancer in hospitalized COVID-19 patients.[18]

Although it is known that the growth rate of SSNs is slow,[19] a study by Kakinuma et al.[20] showed a mean period of 3.6 years for the appearance of a solid component in ground-glass lesions in lung cancer screening patients. Thus, it is essential to differentiate inflammatory from noninflammatory lesions accurately. A consensus statement on the management of lung nodules and lung cancer screening during the COVID-19 pandemic was released in 2020,[21] addressing various clinical situations; however, difficulties in correctly differentiating lesions on imaging were not addressed.

Our study has several limitations, including its single-center retrospective design. In addition, the findings on the reviewed images were not compared with those in the initial report, which was written as a nonstructured report. Our convenience sampling from the private health care system is another bias. However, in a recently published lung cancer screening trial conducted in Brazil,[22] no significant differences were found in the incidence of lung cancer, granulomatous disease, and Lung CT Screening Reporting and Data System category 4 nodules between patients in the public and private health care systems.

In conclusion, detection and characterization of pulmonary SSNs on CT scans were hindered during the COVID-19 pandemic, with fewer SSNs being diagnosed in COVID-19 patients than in pre-COVID-19 pandemic patients. However, the differences between the two samples of patients were not significant. Although follow-up CT is not recommended and is not cost-effective for all patients diagnosed with COVID-19, we must consider the possibility of missed proliferative lesions, especially in patients with demographic characteristics that increase the chance of persistent SSNs, such as being over 50 years of age and being female.

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AUTHOR CONTRIBUTIONS

APZ, VBB, RDG, RRR, FTH, LCAJ, JFPS, GSG, and CFA: conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; validation; visualization; and writing, reviewing, and editing of the manuscript. APZ and CFA: supervision. All authors read and approved the final manuscript.

CONFLICTS OF INTEREST

None declared.

DATA AVAILABILITY STATEMENT

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

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