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MINIREVIEWS

Incidental radiological findings suggestive of COVID-19 in asymptomatic patients

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Abstract

Despite routine screening of patients for coronavirus disease 2019 (COVID-19) symptoms and signs at hospital entrances, patients may slip between the cracks and be incidentally discovered to have lung findings that could indicate COVID-19 infection on imaging obtained for other reasons. Multiple case reports and case series have been published to identify the pattern of this highly infectious disease. This article addresses the radiographic findings in different imaging modalities that may be incidentally seen in asymptomatic patients who carry COVID-19. In general, findings of COVID-19 infection may appear in computed tomography (CT), magnetic resonance imaging, positron emission tomography-CT, ultrasound, or plain X-rays that show lung or only apical or basal cuts. The identification of these characteristics by radiologists and clinicians is crucial because this would help in the early recognition of cases so that a rapid treatment protocol can be established, the immediate isolation to reduce community transmission, and the organization of close monitoring. Thus, it is important to both the patient and the physician that these findings are highlighted and reported.

Key Words: Incidental; Asymptomatic COVID-19; Chest computed tomography; Positron emission tomography-computed tomography; Magnetic resonance imaging; Ultrasound; Oncology patients

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Core Tip: Nowadays, the world is confronting a coronavirus disease 2019 (COVID-19) pandemic that has a major global influence on health, social, and economic issues. COVID-19 shows many different presentations with a wide range of severity. Because it is considered the most significant major health epidemic since that of the Spanish flu 100 years ago, the identification of all patterns of disease is extremely critical to protect the community and healthcare workers from such a highly contagious disease. Radiologists must be alert to recognize the different radiographic findings that suggest COVID-19, even in asymptomatic cases, in different imaging modalities.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Infection has a major global influence on social, health, and economic issues. COVID-19 is considered the most significant major health epidemic since the Spanish flu 100 years ago[1]. It first appeared in Wuhan, China, in December 2019 and was officially declared a pandemic by the World Health Organization (WHO) on March 11, 2020, extending rapidly worldwide thereafter and becoming an outbreak. By the end of 2020, more than 78 million people were infected, leading to over 1.7 million deaths[2]. Unlike infections with other coronaviruses, asymptomatic COVID-19 patients are infectious, leading to the rapid spread of infection worldwide[1,3]. The most common modes of transmission of the virus are person-to-person spreading during intimate contact with an infected person (or asymptomatic infected carriers), inhalation of respiratory droplets, and contact with surfaces contaminated with respiratory droplets or aerosols, which can penetrate the lungs through the nose or mouth[2,4,5]. SARS-CoV-2 virus uses the angiotensin-converting enzyme 2 (ACE2) receptor for cell entry. ACE2 receptors are present in high amounts on epithelial cells, which are more predominant in oral mucosa and lungs, than in heart, blood vessels, brain, and other organs, leading to a diversity in the disease presentation[5-8]. The clinical presentation of COVID-19 ranges from asymptomatic to critically ill, and the most common manifestations are mild to moderate respiratory illness, where recovery occurs without requiring special treatment[6-8]. However, many nonspecific symptoms, such as fever, fatigue, shivering, anorexia, headache, olfactory dysfunction and loss of taste, shortness of breath, cough with or without expectoration, dyspnea, chest tightness, diarrhea, nausea, vomiting, abdominal pain, and muscle soreness, overlap with other viral infections[2,5-12]. Despite most patients with COVID-19 complaining of mild symptoms, the death rate is considerable, ranging from 0.3%–13.1%, with more susceptibility to severe forms of the disease in older patients, especially those with underlying disease, such as diabetes mellitus, cardiovascular disease, respiratory disease, hyperlipidemia, obesity, and chronic renal and hepatic disease[4,10,11].

COVID-19 DIAGNOSIS

A confirmed case of coronavirus disease 2019 (COVID-19) is defined by World Health Organisation as a patient with a positive reverse transcription-polymerase chain reaction (RT-PCR) test, irrespective of clinical signs and symptoms[12]. This test directly assesses the viral load from a nasopharyngeal swab, sputum, or endotracheal lavage[13]. It has impressive specificity of up to 100% owing to its specificity to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) genome sequence, but has imperfect sensitivity of 89% (95%CI: 81%–94%)[14]. A positive result denotes the presence of viable virus only, and a negative result does do not rule out COVID-19 infection[13,15]. False-negative RT-PCR results may occur if the test is performed too early or late in infection course, the viral load is insufficient, or the specimen is of poor quality and also due to technical errors or inappropriate handling and shipping of the specimen. False-positive results may occasionally occur due to technical errors or reagent contamination[14,16,17]. The turnaround time for an RT-PCR test ranges from 50 min to 4 h for semi- to fully automated, walk-away assays and 6–14 h for manually performed assays[12,13,18].

More than 50% of patients with a positive RT-PCR test may be asymptomatic at the time of testing only or throughout the entire duration of the disease, leading to more spread of the virus. Accordingly, it is essential to detect COVID-19 infection at the early stage to immediately isolate the infected person from the healthy population[14,19]. The need for a simple, rapid method to identify asymptomatic patients who need urgent medical or surgical intervention in an emergency and in oncology patients, patients in the intensive care unit, or those who need hospital admission is crucial to prevent the spread of infection. In cases where RT-PCR test results take some time to be available and because this test has imperfect sensitivity, chest radiography is appropriate[8,9,20-23].

CLASSICAL IMAGING CRITERIA OF COVID-19

To prevent the spread of infection in hospital patients or healthcare workers, chest radiography is considered the first-line imaging modality to be performed in patients with suspected coronavirus disease 2019 (COVID-19) or to exclude the presence of COVID-19 infection in patients who need to receive medical or surgical treatment[10,13,17,18,24-29]. Most radiological imaging modalities are beneficial in characterizing COVID-19 infection.

Chest X-ray

Chest X-ray (CXR) findings in COVID-19 patients usually appear at 10–12 d from symptom onset as bilateral lower zone consolidation patches or diffuse airspace opacities with peripheral distribution[10,11,30]. The CXR may be normal in up to 63% of cases, particularly in the early stages[28], and it has a great value in patients with moderate to severe disease who have acute respiratory distress syndrome, showing bilateral diffuse alveolar consolidation that may progress to white lung with or without mild pleural effusion[26,31-33].

Yasin *et al*[7] studied the association of COVID-19 severity and X-ray findings among 350 positive COVID-19 patients. Of them, 62.9% had an abnormal baseline CXR, and the most common findings were consolidation opacities (81.3%), followed by reticular interstitial thickening (39.9%) and ground glass opacities (GGOs) (32.5%). An example of CXR findings in a patient with COVID-19 is presented in Figure 1.

Chest computed tomography

Chest computed tomography (CT) plays a pivotal role in the early detection of COVID-19 pneumonia and has better sensitivity (98%) compared with RT-PCR (89%), particularly in the early course of the disease. However, it also has low specificity (25%) due to the overlap between COVID-19 pneumonia and other types of viral pneumonia[5,8,30,31]. Radiologists must be familiar with the different imaging findings of COVID-19 pneumonia to differentiate it from other types of pneumonia[11,13,30]. Early COVID-19 chest CT findings include bilateral multiple GGOs with a peripheral, subpleural, and posterior distribution, with or without consolidation. In the late phase, the consolidation patches, linear opacities, “crazy-paving” pattern, reversed halo sign, and vascular enlargement become more common[5,9,10,18,32]. The pulmonary histologic findings of COVID-19 resemble those of other coronavirus infections, such as severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) and Middle East respiratory syndrome coronavirus (MERS-CoV)[4], which also shows similarities in chest CT findings[23,33,34]. Great variability is observed in chest CT findings in COVID-19 patients according to the stage and severity of the disease[6,9,15,24,25,35,36]. The Radiological Society of North America classifies the chest CT findings into four categories related to COVID-19 diagnosis: (1) Compatible with viral pneumonia; (2) Indeterminate; (3) Atypical (suggestive of other diagnoses); and (4) No evidence of pneumonia[37].

The Fleischner Society[38] recommends performing a chest CT in moderate to severe infections presenting with hypoxemia and moderate to severe dyspnea, regardless of the RT-PCR test result [39], while RT-PCR is indicated if incidental findings on CT suggest the presence of viral pneumonia[14,19,34,38,39]. Chest abnormalities associated with COVID-19 may be incidentally detected in the visualized lung

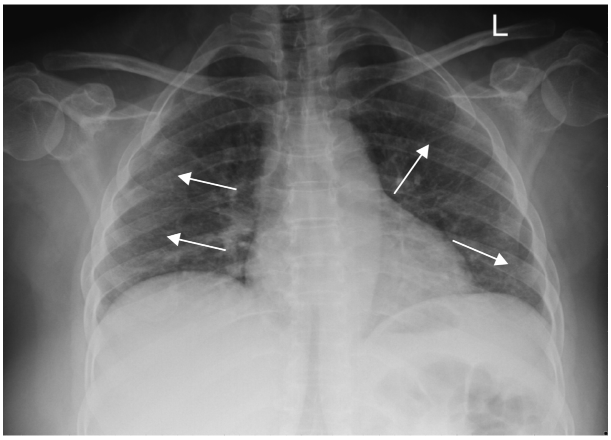

Figure 1 Postero-anterior chest X-RAY in one asymptomatic patient with coronavirus disease 2019 pneumonia from our institution. It shows Interstitial infiltrates and ill-defined, patchy, peripheral opacities in bilateral lung fields.

parenchyma in CT examinations of other body regions, such as in the lower lung base in abdominal CT (Figure 2), the lung apex in head and neck CT studies (Figure 3), and the lung tissues seen in dorso-lumbar spine CT[18,40]. Several studies have been published reporting incidental chest CT findings of COVID-19 in the visualized lung parenchyma in patients with acute abdomen without respiratory manifestation who undergo abdominal CT in the scenario of an acute pandemic[41-47](Table 1).

Lung ultrasound

A lung ultrasound (US) in COVID-19 pneumonia is usually performed using a portable US machine at the bedside to minimize the spread of infection to other patients and healthcare workers[48]. The classical appearance is bilateral irregular pleural lines, subpleural consolidation, areas of thick white lung tissue, and thick irregular vertical artifacts suggesting interstitial alveolar damage[48-50]. In the pediatric age group, lung US has an advantage over CT because it does not use ionizing radiation. Vertical artifacts (70%) and pleural irregularities (60%) were the most common abnormalities detected in 10 symptomatic pediatric patients with confirmed COVID-19 who underwent a chest US while awaiting RT-PCR results Notably, pleural effusions were absent in all 10 patients[44,50,51]. The follow-up of lung US findings to monitor pulmonary involvement in symptomatic COVID-19 patients is preferable to the use of repeated CT scans, especially in critically ill patients or patients on a ventilator, owing to the difficulty in transporting such patients to the CT equipment[5,8,50]. Additionally, US can detect pneumothorax and other complications. However, a major disadvantage is the prolonged close exposure of the operator to the infection and also the need for careful sterilization of the device and the use of transducer and keyboard covers[10]. No reports about incidental lung US findings are available because this is not a routine examination, and it is only performed in certain circumstances.

Magnetic resonance imaging

Although magnetic resonance imaging (MRI) plays no role in the diagnosis of COVID-19 pneumonia, there are many reports of the detection of incidental COVID-19 in MRIs performed for other diagnostic purposes in asymptomatic patients[8,40,42]. After an extensive review of the literature, we found many cases of reported COVID-19 findings in upper lung cuts that appear in brain, neck, and cervico-dorsal spine MRIs and in lower cuts in abdomen and liver MRI studies[4,52-55]. COVID-19 infection appears as peripheral areas of high signal on T2-weighted short tau inversion recovery imaging caused by edema or alveolar opacities. A high T1 signal is observed due to higher tissue density, and partial alveolar collapse with focal areas of restricted diffusion is observed on diffusion-weighted imaging because of increased cell density from the inflammatory reaction. Partial collapse with a heterogeneous enhancement pattern is observed after contrast administration. Thus, radiologists should be alert and look carefully for these findings[34,42,54-56]. Figure 4 shows an example of cardiac MRI findings in a COVID-19 patient. Ates *et al*[52] studied thorax CT and MRI findings in 32 COVID-19 patients who underwent chest CT and then MRI within 24 h after the chest CT. They reported that MRI had a sensitivity of 91.67% and a specificity

Table 1 Summary of incidental asymptomatic COVID-19 studies

Ref.	Imaging modality used	Number of incidental asymptomatic COVID-19 cases/total number of cases	Setting
Ali *et al*[41]	^{18}F-FDG PET-CT	87/764; only 3 of which were RT-PCR negative	Asymptomatic oncology patient
Ferrando-Castagnetto *et al*[47]	^{18}F-FDG PET-CT	1	COVID-19 asymptomatic cancer patient for routine oncological indication
Pallardy *et al*[44]	^{18}F-FDG PET-CT	20/529	COVID-19 asymptomatic cancer patients for routine oncological indication
Wakfie-Corieh *et al* [68]	^{18}F-FDG PET-CT	23/1079, only 14 of which were RT-PCR positive	COVID-19 asymptomatic cancer patients for routine oncological indication
Mo *et al*[66]	^{18}F-FDG PET-CT	1	COVID-19 asymptomatic cancer patients for routine oncological indication
Franceschi *et al*[67]	^{18}F-FDG PET-CT	1	Asymptomatic diffuse large B-cell lymphoma patient
Setti *et al*[64]	^{18}F-FDG PET-CT	5/13	COVID-19 asymptomatic cancer patients
Albano *et al*[65]	^{18}F-FDG PET-CT	6/65 patients	COVID-19 asymptomatic oncology patient
	SPECT-CT	1/12 patients	Asymptomatic patient with treated differentiated thyroid carcinoma
Angelini *et al*[42]	Whole-body MRI	1	COVID-19 asymptomatic multiple myeloma patient under follow-up
Deen *et al*[57]	Liver MRI (basal chest cuts)	1	Emergency patient with hepatic focal lesion
Di Girolamo *et al*[43]	MRI of the abdomen	1	COVID-19 asymptomatic cancer patient for routine oncological indication
Ap Dafydd *et al*[22]	Chest CT	9/240 of CTs were reported as abnormal, only one of which was RT-PCR positive.	Asymptomatic patients prior to major thoracic or abdominal surgery
Siegel *et al*[59]	CT of the abdomen and pelvis (basal chest cuts)	3	Patients presented to emergency department with abdominal pain
Ali *et al*[26]	Chest CT (for other causes)	44	COVID-19 asymptomatic cases
Hyne *et al*[60]	Cerebral angiography	1	Patient presented to emergency department with neurological manifestations

COVID-19: Coronavirus disease 2019; FDG-PET/CT: Fluorodeoxyglucose-positron emission tomography-computed tomography; SPECT/CT: Single photon emission computed tomography; MRI: Magnetic resonance imaging.

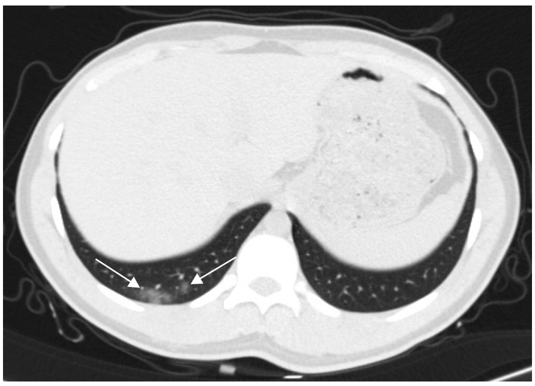

Figure 2 Axial-basal chest cut in urinary tract computed tomography in a patient presenting with renal colic at our institution who was diagnosed with asymptomatic coronavirus disease 2019 due to the presence of peripheral small focal areas of ground glass veiling.

of 100%. Furthermore, rapid limited study using a T2-weighted spin echo sequence, which is widely available in all scanners and can detect GGOs or consolidative patches with no exposure to radiation, was suggested. Angelini *et al*[42] reported a case of incidental COVID-19 pneumonia in a 60-year-old male with multiple myeloma and negative respiratory symptoms who underwent whole-body MRI as routine follow-

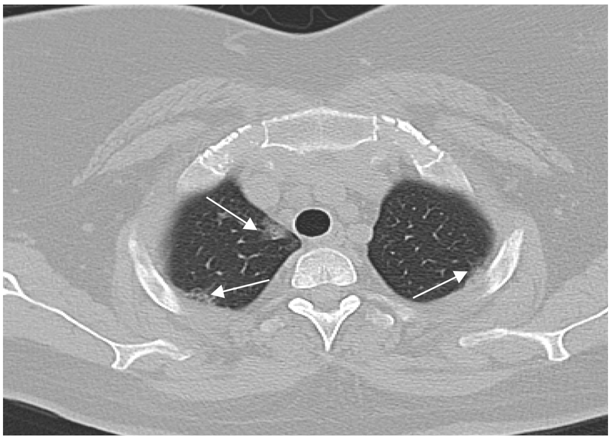

Figure 3 Axial-apical chest cut in brain computed tomography in a patient presenting with head trauma at our institution who was diagnosed with asymptomatic coronavirus disease 2019 due to the bilateral presence of multiple peripheral small foci of ground glass veiling with mild interstitial thickening.

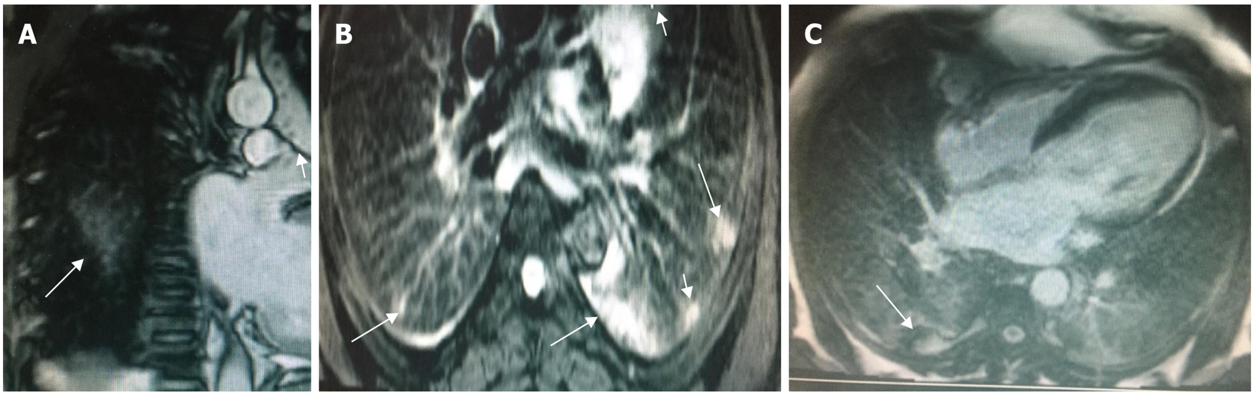

Figure 4 Cardiac magnetic resonance images of a patient with coronavirus disease 2019 who presented to our institute for a viability study showing multifocal peripheral areas of abnormal signal in both lungs that appear as high signal intensity areas localized in the coronal plane (A), high T2 signals (B), and faint heterogenous enhancement in post-contrast sequences (C).

up. The COVID-19 pneumonia presented as peripheral posterior GGOs in the lung in T2-weighted sequences. Deen *et al*[57] reported the detection of incidental basal lung lesions on liver MRI in a 49-year-old woman with a negative RT-PCR result for COVID-19 who presented at the emergency department with vague symptoms. An abdominal US revealed a liver mass, and subsequent MRI examination identified it as a hemangioma, while the scanned lung base showed peripheral high T2-weighted focal areas with restricted diffusion in the left lower lobe. Consequently, the patient underwent a chest CT that confirmed presence of bilateral multiple GGOs. Di Girolamo *et al*[43] reported a 71-year-old woman with T4a colorectal cancer who underwent an abdominal MRI for routine follow-up of hepatic metastasis that led to the incidental detection of bilateral lower lobe GGOs in the scanned lung. Thereafter, the patient underwent RT-PCR, which confirmed that they were positive for COVID-19. MRI can help in the early recognition of cases so that a rapid treatment protocol can be established, the immediate isolation to reduce community transmission, and the organization of close monitoring. Thus, it is important to both the patient and the physician that these findings are highlighted and reported.

ASYMPTOMATIC COVID-19 PATIENTS IN ELECTIVE AND EMERGENCY SURGERIES

On April 15, 2020, the Royal College of Surgeons and Royal College of Radiologists published guidelines on the use of preoperative reverse transcription-polymerase chain reaction (RT-PCR) and chest computed tomography (CT) during the coronavirus disease 2019 (COVID-19) pandemic to exclude COVID-19 infection before elective surgery. These guidelines aim to eliminate the risk of COVID-19-related complications after elective surgery and prevent the transmission of COVID-19 to other patients and healthcare workers[22]. The major obstacle in the management of acute surgical conditions in both urgent and elective surgery is the increased risk of nosocomial transmission. Chetan *et al*[58] evaluated chest CT screening for COVID-19 in a total of 439 elective and emergency surgical patients. The elective surgical cohort included 156 patients who underwent preoperative low-dose unenhanced chest CT, and the emergency surgical cohort included 283 patients with abdominal emergencies where the preoperative abdominal CT was extended cranially to include the lungs from below the carina. Of the 432 patients, 32 (7%) showed potential COVID-19-related lung changes[58]. These findings changed surgical management in the elective surgical cohort only and not in the acute abdominal emergency cohort requiring surgery. On the other hand, Ap Dafydd *et al*[22] assessed the role of chest CT in screening for asymptomatic COVID-19 infection in self-isolating patients before elective oncological surgery. They concluded that preoperative chest CT was unhelpful and might introduce an unnecessary delay. Siegel reported suspected incidental COVID-19 findings in the lung bases in abdominal CT, which raised the possibility of the transmission COVID-19 to the clinician[59]. Thus, direct communication between the radiologist and the referring physician is the first step to protect both patients and healthcare workers against the spread of infection. Furthermore, the authors documented the possibility of viral pneumonia being used as a broad term that helps in decision-making. Hynes *et al*[60] detected incidental peripheral GGOs in the upper lobes of both lungs, which were characteristic of COVID-19 pneumonia, in a 97-year-old female patient who presented with stroke. She underwent arch-to-vertex CT angiography, which was negative for acute stroke. Sun *et al*[8] performed a systematic review and meta-analysis of chest imaging findings in patients with COVID-19. They concluded that chest CT had a low specificity in differentiating COVID-19 pneumonia from other types of pneumonia and recommended that COVID-19 diagnosis be confirmed by clinical and laboratory examinations. Dedeilia *et al*[61] reported that COVID-19 had a major effect on pediatric surgery, because children with COVID-19 are usually asymptomatic or have mild symptoms. Furthermore, many upper respiratory infections in children, such as influenza virus, rhinovirus, and others, present the same symptoms as COVID-19, and coinfection of SARS-CoV-2 may also occur[4,28,62]. Thus, the surgical committee must follow established guidelines to facilitate the workflow and prevent virus transmission, and every patient should be tested by RT-PCR. However, if rapid intervention is crucial in an emergency and RT-PCR results are not available soon enough, the assessment can be based on clinical conditions and/or chest imaging findings [7,22,60].

The guidelines for preoperative COVID-19 testing for elective cancer surgery of 15 April, 2020, were updated on May 14, 2020, to document accumulating evidence that preoperative chest CT screening does not add to the detection of COVID-19 in asymptomatic, isolated, and tested patients and is not recommended for screening before elective cancer surgery[58]. Thus, chest CT should only be considered for screening in preoperative planning in asymptomatic patients who are not isolated when RT-PCR test results are unavailable.

ASYMPTOMATIC COVID-19 ONCOLOGY PATIENTS

Oncology patients are a very special group of because of their high vulnerability to infections caused by risk factors due to their impaired immune systems, such as leukopenia, long-lasting immunosuppression (steroids, antibodies), or low immunoglobulin levels[63]. Oncology patients infected with COVID-19 may present as asymptomatic or with nonspecific symptoms, like fever, cough, dyspnea, fatigue, myalgia, and headache[49,64]. Also, because oncology patients need to continue their treatment, especially in newly discovered cases or patients receiving their treatment as chemotherapy, radiotherapy, or other forms, the benefit: risk ratio of cancer treatment may need to be reconsidered in certain patients[49,65,66]. Some reports are describing the accidentally discovered COVID-19 signs in different imaging modalities performed within the context of following cancer patients. However, the most attractive data was related to the use of fluorodeoxyglucose (FDG) positron emission tomography-CT (PET-CT) imaging, which demonstrates the increased uptake across a variety of pathological etiologies, including infections, inflammatory processes, and neoplasms. Thus, FDG PET-CT imaging plays a role in localizing foci of infection and inflam-

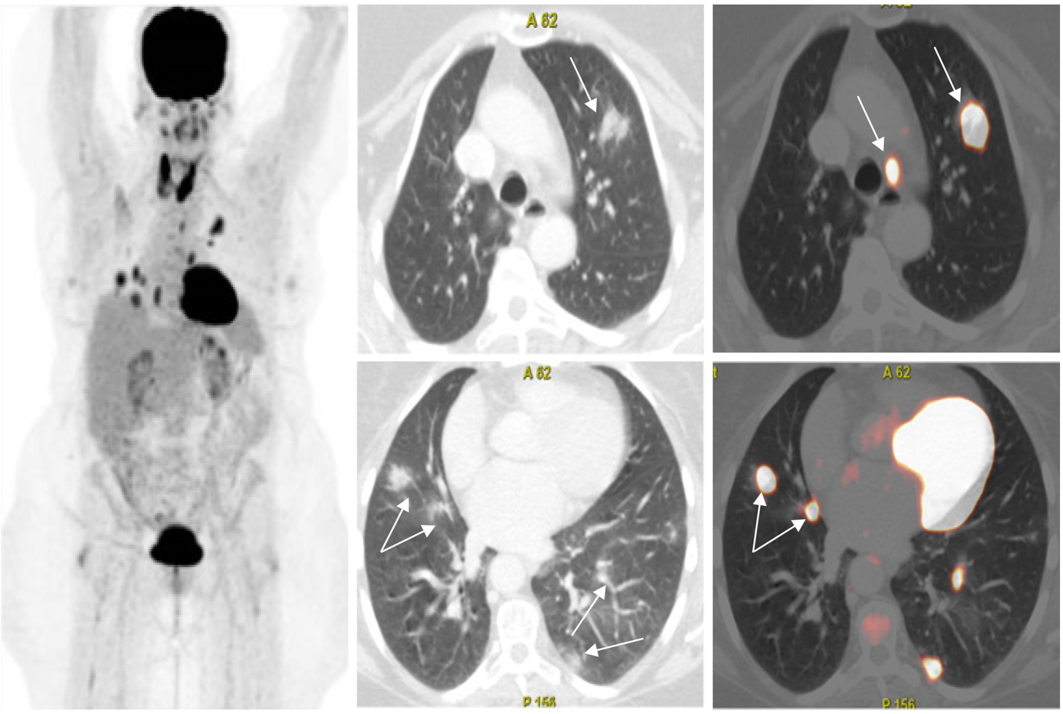

Figure 5 Axial fused thoracic ^{18}Fluorodeoxyglucose-positron emission tomography-computed tomography showing multiple variable-sized metabolically active and mainly subpleural subsegmental consolidative lesions with an SUV$_{max}$ of up to 10.9 as well as metabolically active lymph node seen in the aorto-pulmonary window in a patient with thyroid cancer and asymptomatic coronavirus 2019.

mation in cases of fever of unknown origin. PET-CT permits detailed evaluation of both functional and anatomical/pathological processes[58,44]. Albano *et al*[65] reported a case series performed in the nuclear medicine units in Northern Italy from March 16–24, 2020. This included 65 asymptomatic patients referred for PET-CT with no suspicion of COVID-19 infection. Of them, six (9%) showed ^{18}F-FDG-avid interstitial pneumonia, suggesting COVID-19 infection. The study also included 12 patients who were admitted for whole-body ^{131}I scintigraphy followed by single photon emission CT 3–4 d after radioiodine administration, and 1 of these patients showed peripheral GGOs, suggesting COVID-19 infection, but not an increase in radioiodine uptake. All of the patients with findings suggestive of COVID-19 infection were confirmed positive upon further workup. Mo *et al*[66] reported similar findings in another asymptomatic 60-year oncology patient in the United States with human papillomavirus, and Franceschi *et al*[67] reported a similar scenario in an asymptomatic 61-year-old patient with treated primary diffuse large B-cell lymphoma. Wakfie-Corieh *et al*[68] retrospectively reviewed 1079 oncologic ^{18}F-FDG PET-CT scans performed between February 2 and May 18, 2020 to identify lung and extraparenchymal lung involvement in asymptomatic cancer patients with COVID-19. The authors concluded that FDG PET-CT-positive findings were usually limited to thoracic structures, and silent, distant involvement was infrequent. An example of PET-CT findings in COVID-19 infection is shown in Figure 5. Another retrospective review discussed the incidental findings suggestive of COVID-19 in asymptomatic cancer patients in France who underwent ^{18}F-FDG PET-CT from January 1 to February 21, 2020, in the era before COVID-19 (n = 867 PET-CT scans) and from March 16 to April 17, 2020, in the era of socially spread COVID-19 (n = 529 PET-CT). They noticed a 1.6% increase in parenchymal lung changes during the COVID-19 era[44].

Infection with COVID-19 may remain asymptomatic and appears as incidental findings in nuclear imaging procedures performed for standard oncologic indications [63-67]. PET-CT findings are considered sensitive for the detection of early COVID-19 infection, even before its detection as nasal viral carriage[41,55,66]. It appears in ^{18}F-FDG PET-CT as multiple areas of GGOs showing increased FDG uptake (SUV$_{max}$ is usually around 5.5)[41,55,66]. Some theories explain the FDG activity detected in COVID-19 pulmonary lesions is the result of viral replication after the viral particles penetrate the cells. This replication starts to overwhelm the cellular structure, inciting a proinflammatory state that disrupts the infected and adjacent endothelium, leading to increased FDG uptake[67].

Landete *et al*[28] reported some correlation between the degree of FDG uptake in pulmonary lesions and COVID-19 infection, which may be used as a predictor for the recovery time because the patients with pulmonary lesions had a higher SVU_{max} and took longer to recover. However, a larger sample size is necessary to confirm the predictive value. Many authors did not recommend the use of PET-CT as a primary diagnostic modality for investigating cases of suspected COVID-19 in the emergency setting because PET is an expensive imaging modality associated with prolonged acquisition times and increased radiation burden in comparison with conventional CXR and chest CT[18,44,56].

Nuclear medicine has no primary role in the diagnosis of COVID-19, yet awareness of the pattern of COVID-19 in this type of patient who is either asymptomatic or in the early stage of the disease before manifestations may have great implications in the further management of oncology patients with underlying immunosuppression, either by malignancy or oncologic therapeutics, because the virus is highly contagious and PET requires a much lengthier time in the unit than most other investigations.

CONCLUSION

In some asymptomatic patients with coronavirus disease 2019 (COVID-19) pneumonia on different radiological tools, reverse transcription-polymerase chain reaction, the definitive test for COVID-19, may be false negative. As community transmission of the COVID-19 increases and isolation restrictions are lifted, incidental findings highly suspicious of COVID-19 pneumonia on imaging modalities of asymptomatic patients may become more common. It is crucial to be aware of such appearances and the difficulties that come with them. Radiologists must be alert to signs of COVID-19 infection in various imaging modalities because many asymptomatic patients present to the radiology department for other reasons and could be already infected with COVID. If it remains unrecognized, these patients can transmit COVID-19 to the community and to healthcare workers.

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MINIREVIEWS

Chest radiological finding of COVID-19 in patients with and without diabetes mellitus: Differences in imaging finding

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Abstract

The pandemic of novel coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Diabetes mellitus is a risk factor for developing severe illness and a leading cause of death in patients with COVID-19. Diabetes can precipitate hyperglycaemic emergencies and cause prolonged hospital admissions. Insulin resistance is thought to cause endothelial dysfunction, alveolar capillary micro-angiopathy and interstitial lung fibrosis through pro-inflammatory pathways. Autopsy studies have also demonstrated the presence of microvascular thrombi in affected sections of lung, which may be associated with diabetes. Chest imaging using x-ray (CXR) and computed tomography (CT) of chest is used to diagnose, assess disease progression and severity in COVID-19. This article reviews current literature regarding chest imaging findings in patients with diabetes affected by COVID-19. A literature search was performed on PubMed. Patients with diabetes infected with SARS-CoV-2 are likely to have more severe infective changes on CXR and CT chest imaging. Severity of airspace consolidation on CXR is associated with higher mortality, particularly in the presence of co-morbidities such as ischaemic heart disease. Poorly controlled diabetes is associated with more severe acute lung injury on CT. However, no association has been identified between poorly-controlled diabetes and the incidence of pulmonary thromboembolism in patients with COVID-19.

Key Words: Diabetes mellitus; COVID-19; Chest X-Ray; Chest imaging using x-ray; Computed tomography of chest

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Core Tip: COVID-19 infection can present as multifocal peripheral airspace changes on chest imaging using x-ray (CXR). Ground-glass opacities are the most common computed tomography finding in coronavirus disease 2019 (COVID-19). Post admission daily bloody glucose readings are a strong predictor for COVID-19 CXR changes that indicate poorer outcomes. Poorly controlled diabetes is associated with increased volumes of ground-glass opacity and consolidation. Diabetes is also linked with endothelial dysfunction and hypercoagulability, which may result in the formation of microvascular thrombi in peripheral segments of lung.

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INTRODUCTION

The world is currently undergoing a significant healthcare crisis due to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic. In March 2020, World Health Organisation declared a pandemic caused by SARs-CoV-2. SARS-CoV-2 was named novel coronavirus disease 2019 (COVID-19). Hospitals in different countries have been overwhelmed with patients suffering from COVID-19. So far, 2.78 million people have died as of 29th March 2021[1].

Diabetes mellitus (DM) is a risk factor associated with severe illness in SARS-CoV-2 infection, precipitating hyperglycaemic emergencies such as diabetic ketoacidosis (DKA) and hyperosmolar hyperglycaemic state (HHS)[2]. A third of deaths in England up to May 2020 related to COVID-19 occurred in people with DM[3]. Patients with DM are more likely to stay longer in hospital[4]. DM can cause a deregulated immune system predisposing to infection; the endothelial angiotensin-converting enzyme 2 (ACE2) receptor responsible for SARS-CoV-2 invasion in human cells has reduced expression in patients of DM, possibly due to glycosylation[5]. Insulin resistance and altered glucose homeostasis have been thought to cause alveolar capillary micro-angiopathy and interstitial fibrosis *via* over-inflammation[6].

A normal chest radiograph does not exclude COVID-19 pneumonia, and no single feature on a radiograph is diagnostic[7]. However, a combination of multifocal peripheral airspace changes often found bilaterally may be present in COVID-19. Due to limited PCR testing capacity in the early d of the pandemic, in addition to its low sensitivity and waiting period of up to 2 d, many clinicians turned to chest computed tomography (CT) for early detection of COVID-19.

Studies have reported the negative predictive value of using CT to be above 90%[8,9]. Chest CT was used to detect subtle radiological changes consistent with COVID-19 in patients where the chest radiograph was reported to be normal or indeterminate. Typical CT findings seen in patients with COVID-19 include peripheral ground-glass opacities (GGO), which progresses to consolidation and interstitial thickening within GGO areas known as ‘crazy paving pattern’[10,11]. These non-specific imaging findings of acute lung injury are indistinguishable from other types of viral pneumonia or interstitial lung diseases, thereby limiting the use of CT as a confirmatory diagnostic test in COVID-19.

This article reviews current literature regarding chest imaging changes in patients with DM affected by COVID-19.

LITERATURE SEARCH

A literature search was conducted on PubMed using the keywords of COVID-19 or Coronavirus; CXR or x-ray or radiograph; CT chest; CTPA or pulmonary embolism or PE; and diabetes mellitus or diabetes within the title or abstract.

Chest Radiography

Studies have shown chest radiographs of patients with DM to have increased bilateral airspace consolidation compared to patients without DM[12,13]. The severity of chest radiograph changes in patients with DM has indicated a significant correlation with mortality, as evidenced in multivariate analysis by Cellina *et al*[14]. Patients with bilateral peripheral alveolar disease (Figure 1) often present at a later stage and have a worse outcome. However, some patients with COVID-19 have preserved lung compliance despite being acutely hypoxaemic, suggesting poorer outcomes result from processes other than alveolar damage[15].

In some studies, DM alone was not associated with an increased risk of intensive care unit admission or death. Still, it was associated with cardiovascular disease as a driver of poorer outcomes. Izzi-Engbeaya *et al*[16] studied 889 patients admitted to London hospitals with COVID-19, and their outcomes found patients with DM were found to have a 33% increased risk of death or ICU admission if they also have ischaemic heart disease. Surprisingly, a similar severity of CXR changes was demonstrated for patients with and without DM. Mozzini *et al*[17] (2021) studied 50 Italian patients with COVID-19, 32% of which had DM. Patients with hypertension or DM had 8 times greater risk of having more severe CXR changes.

COVID-19 infection in patients with DM leads to hyperglycaemia, and in some cases leads to DKA and/or HHS[2]. It has been shown that there is a positive correlation between daily average blood glucose readings and CXR findings. Similarly, post-admission day-1 hyperglycaemia was found to be the strongest independent predictor for COVID-19 CXR changes. This was a stronger predictor than age, body mass index, and temperature[18].

Chest computed tomography

Earlier studies employed semi-quantitative methods to analyse chest computed tomography (CT) findings (Figure 2) in patients with COVID-19[19,20]. This involved a single, or multiple experienced radiologists blinded to clinical parameters and assigning a score based on the severity of findings. Higher chest CT scores have been found in patients with DM, suggesting more severe COVID-19 pneumonia when compared with patients without DM[19]. Findings by Iacobellis *et al*[18] suggested day-1 hyperglycaemia as a predictor of COVID-19 severity on CXR were confirmed on CT.

Patients with poorly-controlled DM are likely to have more severe COVID-19 pneumonia. A recent study by Lu *et al*[21] using a quantitative artificial intelligence algorithm found parameters including the percentage of ground glass volume (PGV) and percentage of consolidation volume (PCV), positively correlated with fasting blood glucose and HbA1c. Unlike semi-quantitative methods, results using this approach were not affected by inter- and intra-observer variability. Raoufi *et al*[20] used a semi-quantitative method to study 117 patients with DM in Iran and found no significant difference in patients with well-controlled (defined as maintaining glycaemic variability between 3.9-10 mmol/L) and poorly-controlled DM. However, the poorly-controlled group contained almost 4 times the number of patients (93 *vs* 24). Furthermore, the median age of patients in the well-controlled group were older (75 *vs* 62 years) which may have been a confounding factor for this negative result[20].

Studies have shown mortality rates to be higher among patients with poorly-controlled DM and COVID-19 than the general population with COVID-19[22,23]. In particular, high HbA1c levels have been linked with inflammation and hypercoagulability, resulting in an increased mortality rate in patients with DM suffering from COVID-19[24]. However, the accuracy of these results may be influenced by other co-morbidities such as ischaemic heart disease and stroke. No large-scale studies have yet shown an association between worse CT findings and mortality in DM.

A high incidence of venous and arterial thrombotic complications in critically ill patients with COVID-19 has been reported previously[25]. Recent literature based on autopsy studies shows that the origin of thrombotic lesions in COVID-19 is largely unknown. Lung histopathological analysis found multiple thrombi in small to medium pulmonary arteries giving rise to the theory of COVID-19 associated immunothrombosis, contrary to the conventional thromboembolic pathomechanism of PE [26,27]. In situ microvascular thrombosis or immunothrombosis occurs due to alveolar injury, inflammatory storm and disruption of the thromboprotective pulmonary vascular endothelium. COVID-19 clinical outcomes are worse in patients with diseases associated with endothelial dysfunction such as systemic hypertension, DM and obesity[28].

Figure 1 The Chest X-Ray demonstrates multiple bilateral peripheral predominant airspace opacities. There is no pleural effusion.

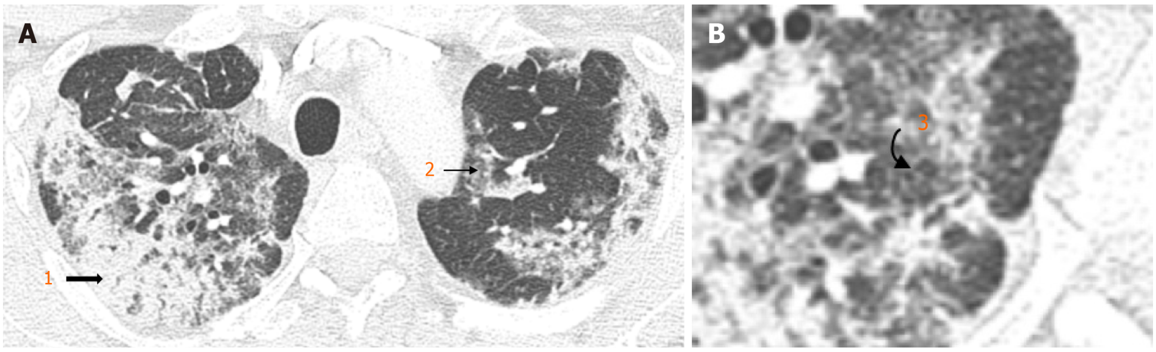

Figure 2 Chest X-Ray. A: Typical appearances of COVID-19 infection: Bilateral peripheral consolidation (1. block arrow), multifocal groundglass opacities (2. straight arrow); B: Some areas of smooth intralobular septal thickening (3. curved arrow).

The radiological finding of subsegmental or segmental thrombi in peripheral segments of lung affected by acute lung injury and the absence of deep vein thrombosis (DVT) in patients with COVID-19 infection, assumes the theory of immunothrombosis[27]. Monfardini *et al*[29] found 76% of patients with a moderate-high pre-test probability of PE and positive D-dimer level (a fibrin degradation product measured to help diagnose thrombosis), had positive CTPA findings. Nevertheless, only 15% of these patients were associated with ultrasound detected lower limb DVT[29], suggesting the remainder probably represented immunothrombosis. A meta-analysis of twenty-seven studies by Suh *et al*[30] revealed DVT was only found in 42% of patients with PE.

As yet, no large-scale studies have reported a link between pulmonary thromboembolism and DM in patients with COVID-19. Kaminetzky *et al*[31] found patients with DM were significantly less frequently observed to have CTPA examinations. Of 23 patients identified to have PE in this study, only 3 had DM; however, this finding may be attributed to the small sample size.

CONCLUSION

DM predisposes to immune deregulation and reduced expression of the ACE2 receptor, leading to severe acute lung injury[5,6]. Studies have proven a link between DM and more severe airspace consolidation based on chest x-ray findings[12,13]. Furthermore, CXR evidence suggests DM is associated with higher mortality in COVID-19. The exact pathogenesis of this is unclear but may be related to microvascular immunothrombosis[26,28].

There is now quantitative evidence to suggest poorly controlled DM is associated with more severe lung injury on CT[21]. However, no large-scale studies have investigated a direct link between CT findings and mortality in DM. Although the incidence of PE is greater in critically ill patients with COVID-19[25], no link has been established between poorly controlled DM and the risk of PE.

As new research into COVID-19 is produced and evidence emerges from autopsy studies, the understanding of pathobiology of the disease has evolved. However, there remains scope for future research; particularly whether small pulmonary thromboses represent venous thromboembolism, immunothrombosis, or a combination of both. Furthermore, a direct link between DM and immunothrombosis may help to guide future management strategies.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Effect of training on resident inter-reader agreement with American College of Radiology Thyroid Imaging Reporting and Data System

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Institutional review board statement: This retrospective, single-institution observational study was approved by the institutional Health Research Ethics Board (Pro 00104708).

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Abstract

BACKGROUND

The American College of Radiology Thyroid Imaging Reporting and Data System (ACR TI-RADS) was introduced to standardize the ultrasound characterization of thyroid nodules. Studies have shown that ACR-TIRADS reduces unnecessary biopsies and improves consistency of imaging recommendations. Despite its widespread adoption, there are few studies to date assessing the inter-reader agreement amongst radiology trainees with limited ultrasound experience. We hypothesize that in PGY-4 radiology residents with no prior exposure to ACR TI-RADS, a statistically significant improvement in inter-reader reliability can be achieved with a one hour training session.

AIM

To evaluate the inter-reader agreement of radiology residents in using ACR TI-RADS before and after training.

METHODS

A single center retrospective cohort study evaluating 50 thyroid nodules in 40 patients of varying TI-RADS levels was performed. Reference standard TI-RADS scores were established through a consensus panel of three fellowship-trained staff radiologists with between 1 and 14 years of clinical experience each. Three PGY-4 radiology residents (trainees) were selected as blinded readers for this study. Each trainee had between 4 to 5 mo of designated ultrasound training. No trainee had received specialized TI-RADS training prior to this study. Each of the readers independently reviewed the 50 testing cases and assigned a TI-RADS score to each case before and after TI-RADS training performed 6 wk apart. Fleiss kappa was used to measure the pooled inter-reader agreement. The relative diagnostic performance of readers, pre- and post-training, when compared

dataset is available from the corresponding author at yang.du@usask.ca. Consent for data sharing was not obtained but the presented data are anonymized and risk of identification is low.

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against the reference standard.

RESULTS

There were 33 females and 7 males with a mean age of 56.6 ± 13.6 years. The mean nodule size was 19 ± 14 mm (range from 5 to 63 mm). A statistically significant superior inter-reader agreement was found on the post-training assessment compared to the pre-training assessment for the following variables: 1. "Shape" (k of 0.09 [slight] pre-training *vs* 0.67 [substantial] post-training, P < 0.001), 2. "Echogenic foci" (k of 0.28 [fair] pre-training *vs* 0.45 [moderate] post-training, P = 0.004), 3. 'TI-RADS level' (k of 0.14 [slight] pre-training *vs* 0.36 [fair] post-training, P < 0.001) and 4. 'Recommendations' (k of 0.36 [fair] pre-training *vs* 0.50 [moderate] post-training, P = 0.02). No significant differences between the pre- and post-training assessments were found for the variables 'composition', 'echogenicity' and 'margins'. There was a general trend towards improved pooled sensitivity with TI-RADS levels 1 to 4 for the post-training assessment while the pooled specificity was relatively high (76.6%-96.8%) for all TI-RADS level.

CONCLUSION

Statistically significant improvement in inter-reader agreement in the assigning TI-RADS level and recommendations after training is observed. Our study supports the use of dedicated ACR TI-RADS training in radiology residents.

Key Words: Thyroid; Thyroid nodule; American College of Radiology Thyroid Imaging Reporting and Data System; Inter-reader agreement; Ultrasound

Core Tip: There is a statistically significant improvement in inter-reader agreement among radiology trainees with limited ultrasound experience using the American College of Radiology Thyroid Imaging Reporting and Data System (TI-RADS) after training for TI-RADS grading and recommendations. This study demonstrates the learnability of TI-RADS in radiology trainees.

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INTRODUCTION

Thyroid nodules are detected in more than 50% of healthy individuals with approximately 95% representing asymptomatic incidental nodules[1-3]. Moreover, an increasing number of thyroid nodules are being detected in recent years on account of improved quality and increased frequency of medical imaging[4]. Although most thyroid nodules are benign and do not require treatment, adequate characterization is necessary in order to identify potentially malignant nodules[1-3]. The American College of Radiology Thyroid Imaging Reporting and Data System (ACR TI-RADS) was therefore introduced to standardize the ultrasound characterization of thyroid nodules based on 5 morphologic categories (composition, echogenicity, shape, margins, and echogenic foci). A TI-RADS score is obtained to represent the level of suspicion for cancer and further direct the need for follow-up and/or tissue sampling [5]. First published in 2017, ACR TI-RADS has been widely adopted by many centers worldwide. Studies have shown that ACR-TIRADS reduces unnecessary biopsies and improves consistency of imaging recommendations[6,7].

Despite its widespread adoption, there are few studies available to date assessing the inter-reader reliability of TI-RADS amongst radiology trainees with limited ultrasound experience. A single-institutional study performed in China by Teng *et al* [8] evaluated three trainees with less than three months of ultrasound experience, demonstrating fair to almost perfect agreement amongst readers for TI-RADS categorization, with improved agreement and diagnostic accuracy after training. To our knowledge, no similar inter-reader agreement studies have been performed in North American trainees. The purpose of this study is to evaluate the inter-reader reliability amongst radiology trainees before and after designated TI-RADS training in a North American institution.

MATERIALS AND METHODS

This retrospective, single-institution observational study was approved by the institutional Health Research Ethics Board (Pro 00104708). This study was exempted from obtaining informed consent. A retrospective review of the local Picture Archiving and Communication System (PACS) was performed to identify thyroid ultrasound studies containing thyroid nodules between July 1, 2019 to July 31, 2020. Included cases required at least 1 thyroid nodule (minimal dimension of 5 mm) with both transverse and sagittal still images and cine video recording in at least 1 plane. Nodules with non-diagnostic image quality, incomplete nodule visualization, and absence of a cine clip covering the entirety of the nodule were excluded. The type of ultrasound make, model, or platform were not considered in the selection process.

Eighty consecutive thyroid nodules meeting eligibility criteria were selected by 2 authors (YD, 6 years clinical experience; MB, 3 years clinical experience) from the eligible ultrasound examinations. A single case could include more than one nodule if sufficient imaging was available to meet inclusion criteria for multiple nodules. Still images of each nodule in both transverse and sagittal planes as well as at least 1 cine video clip of the nodule were saved in a teaching file hosted on our institutional Picture Archiving and Communication System. Each nodule and its representative images/cine clips were saved separately. If a single patient had two nodules, the relevant images and cine clips for each nodule were saved as separate case numbers. Of these, 50 cases were allocated into the "testing" group and 30 cases into the "training" group. Non-random group selection was performed to allow an approximately even distribution of TI-RADS categories within each group and to prevent under-representation of any category. A steering committee consisting of 2 authors including the principal investigator (YD, MB) attempted to evenly divide cases of differentiating difficulty equally between "testing" and "training" groups. This variable approach was selected over a pathological gold standard in an attempt to reduce referral bias in the "testing" group, a situation likely encountered by Teng *et al* [8] where 61% (245/400) of included nodules were pathologically malignant. The trainees were blinded to the distribution approach of the "testing" group.

All patient identifiers were removed apart from age and gender. All cases were evaluated by a consensus review of 3 independent fellowship-trained board-certified staff radiologists with between 1 and 14 years of clinical experience each (GL, MW, MS). Any disagreement on the scoring of nodules for the ACR TI-RADS level was resolved by re-review and consensus discussion. Findings on the consensus review were recorded and set as the standard of reference. This approach has been used in other recent inter-reader reliability studies assessing ACR Reporting and Data Systems [9].

Three PGY-4 radiology residents (trainees) were selected as blinded readers for this study. Each trainee had between 4 to 5 mo of designated ultrasound training, in addition to non-designated ultrasound training on other rotations throughout their training. No trainee had received specialized TI-RADS training prior to this study. Each of the readers independently reviewed the 50 testing cases and assigned TI-RADS score to each case. The readers were provided with a summary chart detailing the ACR TI-RADS classification as described in the ACR TI-RADS White Paper and had access to an online TI-RADS calculator (https://tiradscalculator.com) at the time of independent review[5]. The readers were instructed to assign TI-RADS points for each category including composition, echogenicity, shape, margins, echogenic foci, and to determine the TI-RADS level and ACR TI-RADS recommendations. The pre-training responses were entered into an online survey generated *via* Google Forms. Four weeks after the readers had completed the pre-training assessment; a one hour-long teaching session including a Microsoft PowerPoint presentation illustrating important features of ACR TI-RADS was provided to the readers along with a Microsoft Word document summarizing common areas of disagreement in nodule characterization[5]. The teaching session provided a step-by-step review of the 5 main sonographic features used for nodule scoring in ACR TI-RADS: (1) Composition; (2)

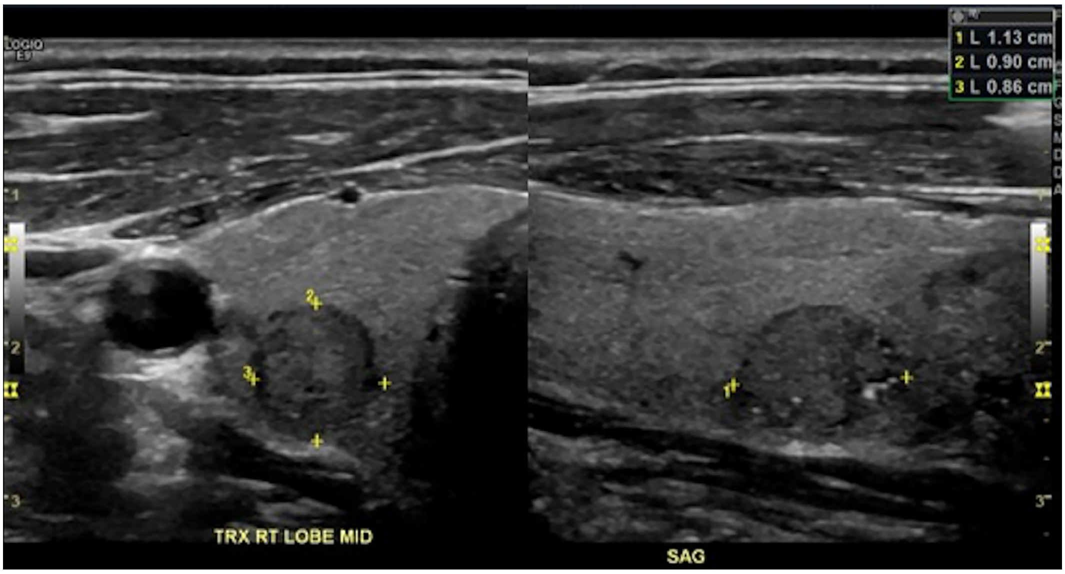

Figure 1 A 51-year-old female with a 1.1 cm × 0.9 cm × 0.9 cm right mid pole thyroid nodule. This nodule was classified correctly with perfect concordance by all 3 readers as solid (+ 2 points), hypoechoic (+ 2 points), taller-than-wide (+ 3 points), smooth margins (+ 0 points), and with punctate echogenic foci (+ 3 points). This had a total points of 10 and a Thyroid Imaging Reporting and Data System level of TR5.

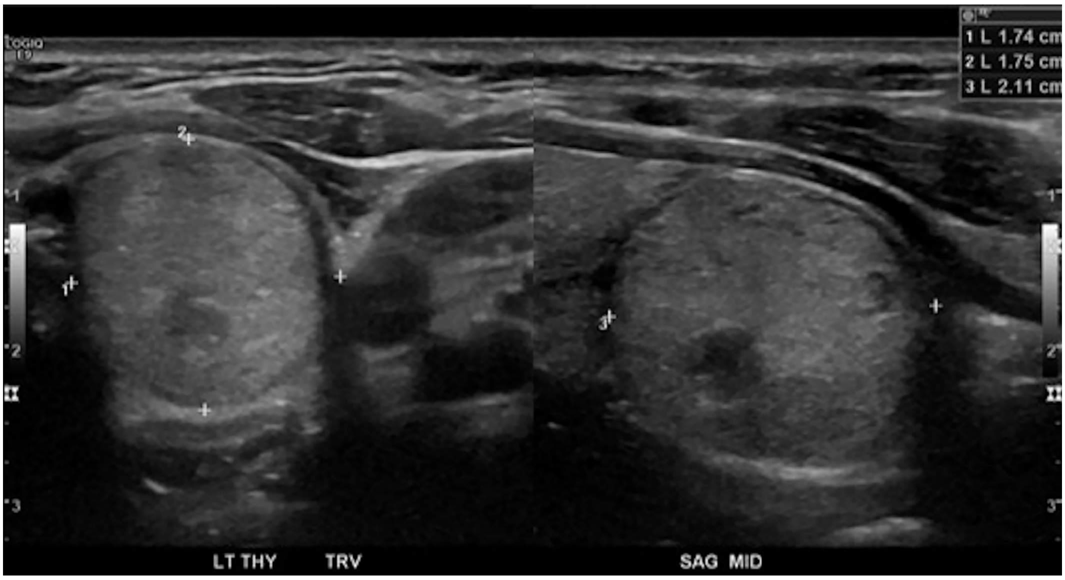

Figure 2 A 45-year-old female with a 1.7 cm × 1.8 cm × 2.1 cm left mid pole thyroid nodule. This nodule was classified by first two readers as Thyroid Imaging Reporting and Data System (TI-RADS) level TR4 and by the third reader as TI-RADS level TR5. The first two readers classified the nodule as solid (+ 2 points), isoechoic (+ 2 points), taller-than-wide (+ 3 points), smooth margins (+ 0 points) and with no echogenic foci (+ 0 points) for a total points of 6 and a TI-RAD level of TR4. For the third reader, a single discrepancy in the scoring of echogenicity as hypoechoic (+ 2 points) rather than isoechoic (+ 1 point) as in the other 2 readers, resulted in a total points of 7 and a TI-RADS level of TR5. As can be seen in the images, the nodule has mixed echogenicity although most of the nodule is isoechoic making this the preferred option.

Echogenicity; (3) Shape; (4) Margin; and (5) Echogenic foci. Each feature's description and interpretation was discussed and illustrated by examples. The readers were given ample opportunity to ask questions, and the consensus panel provided focused clarification to readers in areas of reader uncertainty. Additionally, the trainees were instructed to review the training file that contained the 30 training cases on PACS and corresponding answers were provided for each case. Two weeks after the training session (six weeks after the pre-training assessment), the 50 anonymized cases from the ''testing'' group were re-sent to the readers for independent review. Readers were instructed to re-score the 50 cases and the post-training responses were entered into an online survey generated *via* Google Forms.

Statistical analysis

Categorical variables were expressed as values and percentages. Continuous variables were expressed as the mean ± SD. The following statistical tests were used:

Fleiss kappa (overall agreement) was used to calculate the pooled inter-reader agreement. The kappa (K) value interpretation as suggested by Cohen was used: ≤ 0.20 (slight agreement), 0.21–0.40 (fair agreement), 0.41–0.60 (moderate agreement), 0.61–0.80 (substantial agreement), and 0.81–1.00 (almost perfect agreement)[10].

Paired *t*-test was used to evaluate for significant difference between agreement coefficients[11].

Using the consensus panel as the reference standard, the relative diagnostic parameters (sensitivity, specificity, positive predictive value and negative predictive value) per TI-RADS level were calculated for individual readers and on a pooled basis.

RESULTS

The testing cases comprised of 50 nodules in 40 patients. There were 33 (82.5%) females and 7 males. The mean patient age was 56.6 ± 13.6 years with an age range from 29 to 80 years. Of the 50 nodules, 31 (62%) were located in the right lobe, 18 (36%) in the left lobe and 1 (2%) in the isthmus. The mean nodule size was 19 ± 14 mm with a range from 5 to 63 mm. According to the reference standard that consisted of a consensus panel of 3 fellowship trained staff radiologists, there were 11 (22%) TI-RADS level 1 nodules, 9 (18%) TI-RADS level 2 nodules, 9 (18%) TI-RADS level 3 nodules, 13 (26%) TI-RADS level 3 nodules, and 8 (16%) TI-RADS level 5 nodules.

The pooled inter-reader agreement with the reference standard, pre- and post-training, is listed in Table 1. A statistically significant improvement in reader agreement was demonstrated in post-training inter-reader agreement for nodule shape (P < 0.001), presence of echogenic foci (P = 0.004), TI-RADS level (P < 0.001) and overall recommendation (P = 0.02). Each of these categories improved at least one category of agreement. Only margin characterization remained at slight agreement after training. Similarly, the percentage reader agreement with the reference standard for sonographic features (Table 2), TI-RADS levels (Table 3) and recommendations (Table 4) are also included. Figure 1 provides an illustrated example of complete reader concordance for nodule scoring using ACR TI-RADS. In contrast, Figure 2 provides an illustrated example where there is discordance in reader scoring using ACR TI-RADS.

Finally, the relative diagnostic performance of readers, pre- and post-training, when compared against the reference standard is included in Table 5 and Table 6, respectively. Pre-training pooled sensitivities ranged from 22.3%-66.7% and pooled specificity ranged from 72.2%-95.1%, dependent on TI-RADS category. Post-training pooled sensitivities ranged from 40.7%-63% and pooled specificity ranged from 76.6%-96.8%, dependent on TI-RADS category.

DISCUSSION

The overall inter-reader agreement for ACR TI-RADS should take into account the inter-reader agreement of its two major outcome variables – '*TI-RADS level*' and '*ACR TI-RADS recommendations*'. In our study, the inter-reader agreement for *'TI-RADS level'* showed a significant improvement with training (k = 0.14 (slight) on the pre-training assessment *vs* k = 0.36 (fair) on the post-training assessment)[12]. Our inter-reader agreement for *'ACR TI-RADS recommendations'* also showed a significant improvement with training (k = 0.36 (fair) on the pre-training assessment *vs* k = 0.50 (moderate) on the post-training assessment [P = 0.02]). Our findings suggest that even a single didactic training session can significantly improve the overall inter-reader agreement in radiology residents. Our findings compare favorably with other inter-reader agreement studies involving ACR TI-RADS. A study by Hoang *et al*[7] involving 8 board certified radiologists (2 from academic centers with subspecialty training in US and 6 from private practice with no subspecialty training in US) found a fair (k = 0.35) inter-reader agreement for *'TI-RADS level'*, and moderate (k = 051) inter-reader agreement for *'ACR TI-RADS recommendations'*[7]. Teng *et al*[8] assessed the learnability and reproducibility of ACR TI-RADS in post-graduate freshmen. The study included 3 readers with < 3 mo ultrasound experience and 3 experts with > 15 years ultrasound experience each. The readers independently evaluated 4 groups of nodules

Table 1 Pooled inter-reader agreement with the reference standard

	Pre-training, *k*	Post-training, *k*	*P* value of the difference
Composition	0.46 (95%CI: 0.37 to 0.54), moderate	0.52 (95%CI: 0.44 to 0.61), moderate	0.32
Echogenicity	0.36 (95%CI: 0.29 to 0.44), fair	0.44 (95%CI: 0.37 to 0.52), moderate	0.30
Shape	0.09 (95%CI: 0.02 to 0.21), slight	0.67 (95%CI: 0.56 to 0.78), substantial	< 0.001
Margins	0.03 (95%CI: -0.14 to 0.08), slight	0.05 (95%CI: -0.05 to 0.15), slight	0.71
Echogenic Foci	0.28 (95%CI: 0.19 to 0.37), fair	0.45 (95%CI: 0.36 to 0.53), moderate	0.004
TI-RADS Level	0.14 (95%CI: 0.08 to 0.20), slight	0.36 (95%CI: 0.30 to 0.42), fair	< 0.001
Recommendations	0.36 (95%CI: 0.27 to 0.45), fair	0.50 (95%CI: 0.41 to 0.59), moderate	0.02

Table 2 Percentage reader agreement with the reference standard for sonographic features

Sonographic feature	RS	$R1_{pre}$	$R1_{post}$	$R2_{pre}$	$R2_{post}$	$R3_{pre}$	$R3_{post}$
Composition	*n*	*n* (%)					
Spongiform	4	0 (0)	1 (25)	1 (25)	1 (25)	3 (75)	4 (100)
Cystic or almost completely cystic	11	3 (27.3)	5 (45.5)	7 (63.6)	8 (72.7)	10(90.9)	10(90.9)
Mixed cystic and solid	12	9 (75)	6 (50)	5 (41.7)	7 (58.3)	5 (58.3)	6 (50)
Solid	27	26 (96.3)	26 (96.3)	25 (92.6)	26 (96.3)	18 (66.7)	19 (70.4)
Echogenicity							
Anechoic	11	3 (27.3)	5 (45.5)	5 (45.5)	5 (45.5)	9 (81.8)	8 (72.7)
Hyperechoic or isoechoic	27	23 (85.2)	23 (85.2)	19 (70.4)	21 (77.8)	19 (70.4)	20 (74.1)
Hypoechoic	12	2 (16.7)	4 (33.3)	9 (75)	8 (66.7)	4 (33.3)	4 (33.3)
Shape							
Wilder than tall	42	38 (90.5)	39 (92.9)	7 (16.7)	39 (92.9)	41 (97.6)	40 (95.2)
Taller than wide	8	7 (87.5)	7 (87.5)	7 (87.5)	7 (87.5)	6 (75)	4 (50)
Margins							
Smooth or ill defined	47	36 (76.6)	35 (74.5)	35 (74.5)	33 (70.2)	43 (91.5)	45 (95.7)
Lobulated or irregular	3	1 (33.3)	2 (66.7)	1 (33.3)	2 (66.7)	0 (0)	0 (0)
Echogenic foci							
None or large comet tail artifact	41	20 (48.8)	36 (87.8)	29 (70.7)	39 (95.1)	29 (70.7)	29 (70.7)
Macrocalcification	3	1 (33.3)	1 (33.3)	0 (0)	2 (66.7)	2 (66.7)	2 (66.7)
Punctate echogenic foci	6	5 (83.3)	4 (66.7)	2 (33.3)	5 (83.3)	3 (50)	3 (50)

RS: Reference standard; R1: Reader 1; R2: Reader 2; R3: Reader 3.

with 50 nodules per group. After evaluating each group, a post-group training session was carried out for the freshman. The study found that the inter-reader agreement improved with training. Chung *et al*[13] performed a study evaluating the impact of radiologist's experience on ACR TI-RADS. Six fellowship-trained radiologists were divided into two groups (experienced *vs* less experienced) with the experienced group having at least 20 years of post-fellowship experience each and the less experienced group having 1 year or less of post-fellowship experience each. The study found no significant differences for inter-reader agreement between experienced *vs* less experienced readers for '*TI-RADS level*' or '*ACR TI-RADS recommendations*'. The inter-reader agreement was moderate for both experienced and less experienced groups for '*TI-RADS level*' and moderate to substantial (experienced *vs* less experienced, respectively) for '*ACR TI-RADS recommendations*'. Seifert *et al*[14] evaluated the inter-reader agreement and efficacy of consensus reading for several thyroid imaging risk stratification systems including ACR TI-RADS. The study involved 4 experienced

Table 3 Percentage reader agreement with the reference standard for American College of Radiology Thyroid Imaging Reporting and Data System levels

ACR TI-RADS level	RS, *n*	R1 $_{pre}$, *n* (%)	R1 $_{post}$, *n* (%)	R2 $_{pre}$, *n* (%)	R2 $_{post}$, *n* (%)	R3 $_{pre}$, *n* (%)	R3 $_{post}$, *n* (%)
1	11	1 (9.1)	5 (45.5)	1 (9.1)	7 (63.6)	10 (90.9)	8 (72.7)
2	9	3 (33.3)	4 (44.4)	0 (0)	4 (44.4)	3 (33.3)	3 (33.3)
3	9	4 (44.4)	5 (55.5)	1 (11.1)	6 (66.7)	4 (44.4)	6 (66.7)
4	13	4 (30.8)	5 (38.5)	5 (38.5)	9 (69.2)	5 (38.5)	5 (38.5)
5	8	7 (87.5)	4 (50)	6 (75)	5 (62.5)	3 (37.5)	3 (37.5)

ACR TI-RADS: American College of Radiology Thyroid Imaging Reporting and Data System; RS: Reference standard; R1: Reader 1; R2: Reader 2; R3: Reader 3.

Table 4 Percentage reader agreement with the reference standard for American College of Radiology Thyroid Imaging Reporting and Data System recommendations

Recommendations	RS, *n*	R1 $_{pre}$, *n* (%)	R1 $_{post}$, *n* (%)	R2 $_{pre}$, *n* (%)	R2 $_{post}$, *n* (%)	R3 $_{pre}$, *n* (%)	R3 $_{post}$, *n* (%)
No follow up	25	13 (52)	17 (68)	10 (40)	19 (76)	21 (84)	22 (88)
Follow up	5	3 (60)	1 (20)	1 (20)	3 (60)	3 (60)	3 (60)
FNA	20	17 (85)	15 (75)	18 (90)	17 (85)	11 (55)	13 (65)

RS: Reference standard; R1: Reader 1; R2: Reader 2; R3: Reader 3; FNA: Fine needle aspiration.

specialist readers with more than 5 years of clinical experience each. The readers independently scored 40 thyroid image datasets in session 1 followed by a joint consensus read (C1). After this, the process was repeated with independent scoring of 40 new image datasets in session 2, followed by another consensus read (C2). For ACR TI-RADS, the study found a significantly higher inter-reader agreement for session 2 (k = 0.57, moderate) *vs* session 1 (k = 0.32, fair) [P < 0.01], indicating that the addition of a consensus read had an impact in improving the inter-reader agreement.

Our study also evaluated the inter-reader agreement of individual sonographic features including composition, echogenicity, shape, margins, and echogenic foci. Our findings showed a significant improvement in inter-reader agreement with training for features such as '*shape*' (k = 0.09, slight $_{\text{pre-training}}$ versus k = 0.67, substantial $_{\text{post-training}}$, P < 0.001) and '*echogenic foci*' (k = 0.28, fair $_{\text{pre-training}}$ versus k = 0.45, moderate $_{\text{post-training}}$, P = 0.004) but not for the others. The features with the strongest inter-reader agreement in our study were '*shape*' (k = 0.67 $_{\text{post-training}}$, substantial) and 'composition' (k = 0.52 $_{\text{post-training}}$, moderate). Hoang *et al*[7] also found similar findings in their study with 'shape' (k = 0.61, substantial) and 'composition' (k = 0.58, moderate) having the strongest inter-reader agreement amongst the 5 principal sonographic features. The feature with the poorest inter-reader agreement in our study was margins (k = 0.05 $_{\text{post-training}}$, slight). Similarly, Hoang *et al* [7] also found that 'margins' had the poorest inter-reader agreement (k = 0.25, fair) in their study. The poor inter-reader agreement for 'margins' is not surprising as accurate assessment requires a thorough review of the entire cine clip, rather than review of the still images only. Margins may also be harder to interpret through ultrasound artifacts. Finally, two of the available answer options for 'margins' in ACR TI-RADS are 'ill defined' (TI-RADS + 0 points) and 'irregular' (TI-RADS + 2 points). However, both options share innate conceptual similarities in interpretation and can lead to overlap. The poorest and strongest inter-reader agreement were also matched with the same features identified by Hoang's board-certified radiologists, indicating that the limitation may be inherent to the reporting and data system rather than trainee experience.

We also evaluated the relative sensitivity and specificity of the radiology residents in assigning TI-RADS levels compared to consensus reference standard before and after training. There was a general trend towards improved pooled sensitivity with TI-RADS levels 1 to 4 for the post-training assessment while the pooled specificity was relatively high (76.6-96.8%) for all TI-RADS level. Overall findings suggest that a single didactic training session improves the detection of benign (TI-RADS 1-3) lesions while

Table 5 The relative sensitivity, specificity, positive predictive value, and negative predictive value per Thyroid Imaging Reporting and Data System Level on the pre-training assessment compared to the reference standard

Pre-training, Statistics	TI-RADS 1, %	TI-RADS 2, %	TI-RADS 3, %	TI-RADS 4, %	TI-RADS 5, %
Sensitivity					
R1	9.1 (0.2-41.3)	33.3 (7.5-70.1)	44.4 (13.7-78.8)	30.8 (9.1-61.4)	87.5 (47.4-99.7)
R2	9.1 (0.2-41.3)	0 (0-33.6)	11.1 (0.3-48.3)	38.5 (13.9-68.4)	75 (34.9-96.8)
R3	90.9 (58.7-99.8)	33.3 (7.5-70.1)	44.4 (13.7-78.8)	38.5 (13.9-68.4)	37.5 (8.5-75.5)
Pooled	36.4 (20.4-54.9)	22.2 (8.6-42.3)	33.3 (16.5-54)	35.9 (21.2-52.8)	66.7 (44.7-84.4)
Specificity					
R1	100 (91.0-100)	90.2 (76.9-97.3)	92.7 (80.1-98.5)	62.2 (44.8-77.5)	76.2 (60.6-88)
R2	100 (91-100)	97.6 (87.1-99.9)	80.5 (65.1-91.2)	81.1 (64.8-92)	50 (34.2-65.8)
R3	66.7 (49.8-80.9)	97.6 (87.1-99.9)	95.1 (83.5-99.4)	89.2 (74.6-97)	90.5 (77.4-97.3)
Pooled	88.9 (81.8-94)	95.1 (89.7-98.2)	89.4 (82.6-94.3)	76.6 (67.6-84.1)	72.2 (63.5-79.8)
Positive predictive value					
R1	100	42.9 (16.8-73.6)	57.1 (26.4-83.2)	22.2 (10.3-41.6)	41.2 (27.7-56.1)
R2	100	0	11.1 (1.8-46.8)	41.7 (21.5-65.1)	22.2 (14.8-32.1)
R3	43.5 (32.2-55.5)	75 (26-96.2)	66.7 (30.1-90.3)	55.6 (28.3-79.8)	42.9 (17.1-73.2)
Pooled	48 (31.8-64.6)	50 (25.9-74.1)	40.9 (24.8-59.2)	35 (23.9-48)	31.4 (23.5-40.5)
Negative predictive value					
R1	79.6 (76.4-82.5)	86.1 (79.4-90.8)	88.4 (80.8-93.2)	71.9 (62.2-79.9)	97 (83.5-99.5)
R2	79.6 (76.4-82.5)	81.6 (80.9-82.4)	80.5 (75.8-84.5)	79 (70.4-85.6)	91.3 (75.3-97.3)
R3	96.3 (79.8-99.4)	87 (80.7-91.4)	88.6 (81.2-93.4)	80.5 (72.6-86.5)	88.4 (81.5-92.9)
Pooled	83.2 (79.2-86.6)	84.8 (81.9-87.3)	85.9 (82.3-88.9)	77.3 (72.5-81.5)	91.9 (86.5-95.3)

TI-RADS: Thyroid Imaging Reporting and Data System; RS: Reference standard; R1: Reader 1; R2: Reader 2; R3: Reader 3.

retaining high specificity in radiology residents. Improved identification of benign lesions is critical in avoiding unnecessary biopsies and interventions, a major aim of the ACR TI-RADS system.

The current study has several limitations. One limitation is the lack of a pathological reference standard. The reference standard was an expert consensus review by 3 board certified radiologists with Body Imaging fellowship and 1-14 years of clinical experience. However, it should be noted that this study is designed primarily to evaluate inter-reader reliability of radiology residents, and not the inherent performance of the ACR TI-RADS itself. As such, an expert consensus panel was deemed a practical reference standard, and one that simulates ‘real world’ clinical practice[9]. Another limitation is the relatively small number of cases used. However, even with this limited number of cases, we were able to show statistically significant improvements in inter-reader agreement for the two major outcome variables (TI-RADS level and ACR TI-RADS recommendations). While there is a relatively even distribution of TI-RADS levels among the test cases *via* non-random selection, there is uneven distribution of individual ultrasound features within the group. Of the 50 test cases, only 3 nodules demonstrated ‘lobulated or irregular’ margins (TI-RADS points +2), while the remaining 47 are ‘smooth’ or ‘ill-defined’ (TI-RADS points +0). A larger sample size can improve this and lead to more representative analysis of individual ultrasound features. Finally, training retention over time was not evaluated in this study, with the post-training testing performed two weeks after didactic and training case review.

Table 6 The relative sensitivity, specificity, positive predictive value, and negative predictive value per Thyroid Imaging Reporting and Data System Level on the post-training assessment compared to the reference standard

Post-training, Statistics	TI-RADS 1, %	TI-RADS 2, %	TI-RADS 3, %	TI-RADS 4, %	TI-RADS 5, %
Sensitivity					
R1	45.5 (16.8-76.6)	44.4 (13.7-78.8)	55.6 (21.2-86.3)	38.5 (13.9-68.4)	50 (15.7-84.3)
R2	63.6 (30.8-89.1)	44.4 (13.7-78.8)	66.7 (29.9-92.5)	69.2 (38.6-90.9)	62.5 (24.5-91.5)
R3	72.7 (39-94)	33.3 (7.5-70.1)	66.7 (29.9-92.5)	38.5 (13.9-68.4)	37.5 (8.5-75.5)
Pooled	60.6 (42.1-77.1)	40.7 (22.4-61.2)	63 (42.4-80.6)	48.7 (32.4-65.2)	50 (29.1-70.9)
Specificity					
R1	92.3 (79.1-98.4)	97.6 (87.1-99.9)	90.2 (76.9-97.3)	70.3 (53-84.1)	81 (65.9-91.4)
R2	94.9 (82.7-99.4)	97.6 (87.1-99.9)	95.1 (83.5-99.4)	73 (38.6-90.9)	90.5 (77.4-97.3)
R3	66.7 (49.8-80.9)	95.1 (83.5-99.4)	97.6 (87.1-99.9)	86.5 (71.2-95.5)	90.5 (77.4-97.3)
Pooled	84.6 (76.8-90.6)	96.8 (91.9-99.1)	94.3 (88.6-97.7)	76.6 (67.6-84.1)	87.3 (80.2-92.6)
Positive predictive value					
R1	62.5 (32-85.5)	80 (33.6-96.9)	55.6 (29.4-79)	31.3 (16.3-51.5)	33.3 (16.5-56)
R2	77.8 (45.8-93.6)	80 (33.6-96.9)	75 (41.8-92.6)	47.4 (32.2-63.1)	55.6 (29.9-78.6)
R3	38.1 (25.8-52.2)	60 (22.6-88.5)	85.7 (45.1-97.8)	50 (25.6-74.4)	42.9 (17.1-73.2)
Pooled	52.6 (40.1-64.8)	73.3 (48.6-88.9)	70.8 (52.8-84.1)	42.2 (31.5-53.8)	42.9 (29-57.9)
Negative predictive value					
R1	85.7 (77.6-91.2)	88.9 (81.7-93.5)	90.2 (81.6-95.1)	76.5 (66.8-84)	89.5 (80.7-94.5)
R2	90.2 (80.8-95.3)	88.9 (81.7-93.5)	92.9 (83.7-97)	87.1 (74.5-94)	92.7 (83.7-96.9)
R3	89.7 (76.3-95.9)	86.7 (80.3-91.2)	93 (84.1-97.1)	80 (71.9-86.2)	88.4 (81.5-92.9)
Pooled	88.4 (83.2-92.1)	88.2 (84.5-91.1)	92.1 (87.6-95)	81 (75.5-85.4)	90.2 (85.9-93.2)

TI-RADS: Thyroid Imaging Reporting and Data System; RS: Reference standard; R1: Reader 1; R2: Reader 2; R3: Reader 3.

CONCLUSION

Overall, the current study demonstrates a statistically significant improvement in inter-reader agreement among radiology residents, with no prior ACR TI-RADS experience, in the assignment of TI-RADS level and recommendations after a single didactic teaching session compared to expert consensus. Our study demonstrates the learnability of the ACR TI-RADS system and supports the use of dedicated training in radiology residents. Future studies can also be directed to evaluate the effect of additional training sessions with focus on areas/features demonstrating lower inter-rater agreement such as “margins” and retention of training over time.

ARTICLE HIGHLIGHTS

Research background

Thyroid nodules are common and often incidental. The American College of Radiology Thyroid Imaging Reporting and Data System (ACR TI-RADS) standardizes the use of ultrasound for thyroid nodule risk stratification.

Research motivation

Despite the widespread usage of this system, the learnability of TI-RADS has not been proven in radiology trainees.

Research objectives

To evaluate the inter-reader reliability amongst radiology trainees before and after TI-

RADS training.

Research methods

Three PGY-4 radiology residents were evaluated for inter-reader reliability with a 50 thyroid nodule data set before and after a 1-hour didactic teaching session and review of a training data set, with assessment performed 6 wk apart. Performance was compared to a consensus panel reference standard of three fellowship trained radiologists.

Research results

After one session of dedicated TI-RADS training, the radiology residents demonstrated statistically significant improvement in inter-reader agreement in subcategories of "shape", "echogenic foci", "TI-RADS level", and "recommendations" when compared with expert panel consensus. A trend towards higher pooled sensitivity for TI-RADS level 1-4 is also observed.

Research conclusions

Resident trainees demonstrated a statistically significant improvement in inter-reader agreement for both TI-RADS level and recommendations after training. This study demonstrates the learnability of the ACR TI-RADS.

Research perspectives

A multi-institutional and multi-national assessment of radiology resident diagnostic accuracy and inter-reader reliability of ACR TI-RADS classification and recommendations before and after training would improve the generalizability of these results.

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