LUNG ULTRASOUND

RECOMMENDATION

We suggest against the use of lung ultrasound alone in diagnosing patients with suspected COVID-19 infection. *(Low quality of evidence, Conditional recommendation)*

Consensus Issues

Majority of the panelists voted for a conditional recommendation against lung ultrasound alone due to the low quality of evidence related to its diagnostic accuracy. However, other panelists argued that a strong recommendation should be made against the use of lung ultrasound alone in diagnosing suspected COVID-19 patients since it has not been found to be as accurate as the current gold standard, which is RT-PCR. Lung ultrasound is still considered a valuable prognostic tool to assess clinical deterioration as it can predict the presence of abnormalities in the lung findings of COVID-19 patients.

EVIDENCE SUMMARY

Should lung ultrasound alone be used to diagnose COVID-19 infection among suspected patients?

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Key Findings

Moderate quality evidence from 8 studies showed that the pooled sensitivity of lung ultrasound (LUS) is 88% (95%CI: 79 to 93); I^2 = 70.18 and the pooled specificity of LUS is 63% (95% CI: 47 to 77); I^2 = 89.64. In these studies, the sensitivity of lung ultrasound ranged from 68 to 97% while specificity ranged from 21 to 89%. Overall, lung ultrasound is found to be sensitive but not specific for the diagnosis of COVID-19.

Introduction

Patients who are suspected to have COVID-19 need to be assessed in a timely manner to establish whether they are indeed infected so that they can receive prompt and appropriate care, self-isolate to prevent spread, and to facilitate contact tracing. The current reference standard for the diagnosis of COVID-19 is the reverse transcriptase polymerase chain reaction (RT-PCR) which uses different specimens (i.e., nasal, nasopharyngeal or oropharyngeal). The use of RT-PCR requires sophisticated equipment, trained specialists and may take at least 24 hours to produce results. It is also not completely accurate and may require repeat testing or a different test altogether to confirm the diagnosis [1]. These findings highlight the need to identify tools to enhance or complement the diagnosis of COVID-19.

It has been shown that a consequence of COVID-19 infection is the development of interstitial lung disease which can assessed through different imaging methods, including computed

tomography (CT) scan and lung ultrasound [2]. CT scan is specific in detecting interstitial lung disease but is not readily available in primary care settings. On the other hand, a lung ultrasound is more accessible, can be used at the bedside, and was reported to have high sensitivity and specificity [3]. However, the diagnostic performance of lung ultrasound can also vary depending on the level of experience of the ultrasonographer or reader [4]. The LUS also does not give a comprehensive view of the lung parenchyma, which limits the assessment of deep lung portions and is strongly operator-dependent [5].

Review Methods

We searched several electronic databases (i.e., MEDLINE, CENTRAL) and preprint servers (medRxiv, bioRxiv, ChinaXiv) until April 23, 2021, using the following keywords in free text and MeSH terms: coronavirus, COVID-19, 2018 ncov, novel coronavirus, SARS-CoV-2, suspect, probable, new coronavirus, chest ultrasound, lung ultrasound, thoracic ultrasound, ultrasonography, RT-PCR, polymerase chain reaction, diagnosis, diagnostic value, accuracy, sensitivity and specificity with no language restrictions. We also searched trial registries (i.e., ClinicalTrials.gov, WHO ICTRP, ChiCTR) on April 23, 2021, for ongoing clinical studies.

A pre-specified criteria was set to determine the studies to be included in this evidence review. We included studies that looked into: (1) suspected or probable cases of COVID-19, (2) with available data to construct a 2x2 contingency table for diagnostic accuracy, (3) used chest or lung ultrasound as index test and RT-PCR as the reference standard. We set our exclusion criteria: (1) confirmed cases of COVID-19 at the beginning of the study and (2) case series, case reports, case-control studies.

We appraised the studies using the QUADAS-2 tool and extracted the data from the included studies. Measures of diagnostic accuracy such as sensitivity and specificity values were pooled using STATA version 16. When applicable, we performed subgroup analysis based on (1) criteria of abnormality from lung ultrasound findings, and (2) population (i.e., symptomatic vs. asymptomatic, outpatient or in-patient, and age group, reader level of experience).

Results

Characteristics of Included Studies

Types of studies

Evidence for this review came from 8 observational studies involving a total of 809 patients. These studies were conducted among patients seen in the outpatient or emergency department (ED) covering the period of April to May 2020.

Participants

All studies included adult patients seen at the outpatient or at the ED who were symptomatic and suspected to have COVID-19. Studies were done in different countries including one in Belgium [11], two in Italy [7,9], two in France [6,13], two in the Netherlands [8, 10], and one in the United States [12]. Patients across the studies were recruited within April to May 2020.

Index test and definition of imaging test positivity

The included studies used lung ultrasound (i.e., at point of care) as the index test. Studies reported different scoring systems for determining positive test results for LUS but commonly used the

presence of B-lines or the presence of vertical hyperechoic artifacts departing from the pleura and directing in-depth, representing thickened peripheral interlobular septa.

Reference standard
All studies used RT-PCR as the reference standard for the diagnosis of COVID-19.

Overall quality of evidence
The GRADE quality of evidence for the overall sensitivity was rated moderate (downgraded due to inconsistency) while the overall specificity was rated low (downgraded due to inconsistency and imprecision) (Appendix 4).

Typical LUS Imaging Features
Lung ultrasound findings across the eight studies included detection of B-lines and/or consolidation in two or more zones unilaterally or in one or more zones bilaterally.

Diagnostic Accuracy
Based on the 8 studies (n = 809), the pooled sensitivity of lung ultrasound (LUS) is 88% (95%CI: 79 to 93; I^2 = 70.18) and the pooled specificity of LUS is 63% (95% CI: 47 to 77; I^2 = 89.64). The sensitivity of lung ultrasound ranges from 68 to 97% while specificity ranges from 21 to 89%; lung ultrasound is found to be sensitive but not specific for the diagnosis of COVID-19. Subgroup analyses based on population (i.e., symptomatic vs. asymptomatic, outpatient or in-patient, and age group) were not performed due to lack of studies with adequate data.

We performed exploratory subgroup analyses based on level of reader experience. Among studies (n = 4) with experienced readers [8-11] (i.e., radiologists or with training for LUS), the pooled sensitivity of lung ultrasound (LUS) is 91% (95%CI: 74 to 97) while the pooled specificity of LUS is 59% (95% CI: 33 to 81). In studies with unclear level of reader experience (n = 4) showed that the pooled sensitivity of lung ultrasound (LUS) is 88% (95%CI: 80 to 94) and the pooled specificity of LUS is 64% (95% CI: 56 to 71) [6-7, 12-13].

Recommendations from Other Groups

As of June 11, 2020, the World Health Organization released a rapid advice document on the use of chest imaging in COVID-19 and stated that for symptomatic patients with suspected COVID-19, WHO suggest not using chest imaging (including chest radiography, CT scan, lung ultrasound) for the diagnostic workup of COVID-19 when RT-PCR testing is available with timely results (Low certainty of evidence, conditional recommendation). RT-PCR should be done to confirm diagnosis of COVID-19 [14].

For symptomatic patients with suspected COVID-19, WHO suggests using chest imaging (including chest radiography, CT scan, lung ultrasound) for the diagnostic workup of COVID-19 when: (1) RT-PCR testing is not available; (2) RT-PCR testing is available, but results are delayed; and (3) initial RT-PCR testing is negative, but with high clinical suspicion of COVID-19 (Low certainty of evidence, conditional recommendation). Chest imaging should be used as one element of the diagnostic workup that also includes clinical and laboratory data. [14]

Research Gaps

There are currently six ongoing studies on the use of lung ultrasound to diagnose COVID-19 patients (Appendix 5).

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Appendix 1. Characteristics of Included Studies

Study ID	Country	Study Participants	Age group	Setting	Index test(s)	Definition of index test positivity	Training level of readers	Reference Standard	Proportion of initial negative results with repeat RTPCR
Bar 2020 [6]	France	People with suspected COVID-19 (unclear)	Adults only	Outpatient	Ultrasound of the lungs (POCUS)	Unclear	Unclear	RT-PCR twice, if necessary	1
Dini 2020 [7]	Italy	People with suspected COVID-19 (symptomatic or asymptomatic)	± 70 years of age	Outpatient (LTC)	Ultrasound of lungs (POCUS)	Classification system: non-coalescent B-lines in > 3 zones (score 1), coalescent B-lines in > 3 zones (score 2), and with hyperechoic non-consolidated state (score 3)	Unclear	RT-PCR, no other details provided	Unclear
Fonsi 2020 [9]	Italy	patients with suspected COVID-19, all symptomatic	Adults only	Outpatient	Index test(s): chest CT (non-contrast); ultrasound of lungs (POCUS)	Definition for positive diagnosis on ultrasound: not reported	radiologist	RT-PCR once; twice in some	Unclear
Narinx 2020 [11]	Belgium	patients with suspected	adults, perhaps	Outpatient	chest CT (low dose); ultrasound of	Defintion for positive diagnosis on	radiologist	RT-PCR, no other details provided	Unclear

		COVID-19, all symptomatic	also children		lungs (POCUS)	ultrasound: positive if one or more BLUE points showed a positive B-line parameter			
Pare 2020 [12]	USA	patients with suspected COVID-19, all symptomatic	adults, perhaps also children	Outpatient	Index test(s): chest X-rays; ultrasound of lungs (POCUS)	Definition for positive diagnosis on ultrasound: positive if any Blines were detected.	unclear	RT-PCR once, twice in some	0.25
Haak 2020 [8]	Netherlands	Both patients with COVID-19 as primary reason for ED referral and patients with another main complaint (eg, chest pain, trauma) who were suspected of COVID-19 were eligible for inclusion. Suspicion of COVID-19 was	> 16 years old	ED of our non-academic level 1 trauma centre, convenience sample of 100 patients with suspected COVID-19	ultrasound of the lungs (POCUS)	POCUS was deemed COVID-19 positive when images in at least one zone met the criteria described in Table 1: POCUS of the lungs scoring system for pulmonary manifestations of COVID-19	emergency medicine resident with 2.5 years of POCUS experience	Final diagnosis of COVID-19 was defined as a positive PCR or a positive chest CT result for COVID-19 within 14 days of ED presentation. The CT scan was defined positive according to the COVID-19 Reporting and Data System (CO-RADS) classification when rated '4' or '5' (high or very high level of suspicion of COVID-19) and was obtained	Unclear

		based on any of the following symptoms: fever ≥38°C, cough, dyspnoea, rhinorrhoea, anosmia, sore throat, diarrhoea or abdominal pain.						from the radiology report.	
Peyrony 2020 [13]	France	patients attending the ED who had suspected COVID-19,	all adult patients with suspected COVID-19 who were tested for SARS-CoV-2.	ED	Lung ultrasound	Presence of bilateral B lines	Unclear	The criterion standard for diagnosis was the result of SARS-CoV-2 RT-PCR via nasal swab (Cobas SARS-CoV-2 Test; Roche, Meylan, France). The patients who initially had a negative RT-PCR result in the ED but a positive test result in the next 48 hours were considered as having positive results (initial false negative).	Unclear

Lieveld 2020 [9]	Netherlands	All patients 18 years and older who were referred to the ED for internal medicine with suspected COVID-19	Adult patients	ED	Lung ultrasound	In keeping with pre-specified criteria in recent Chinese, Italian and British literature, LUS was deemed positive if there were three or more B-lines and/or consolidation in two or more zones unilaterally or in one or more zones bilaterally. When COVID-19 features were not found or just in one zone unilaterally, the scan was deemed negative	LUS was performed or supervised by internists (mostly registrars) who were certified in point-of-care ultrasound and had performed at least 20 supervised LUS.	A PCR test on swab samples obtained from the oropharynx or nasopharynx (or if available, from sputum, faeces, tracheal aspirate or bronchoalveolar lavage) was performed in all patients according to WHO standards. The same PCR assay was used in all participating hospitals. In case of a negative or indeterminate test result but a high clinical suspicion, PCR was repeated. If a patient had an indeterminate test and no PCR was repeated, the PCR was considered negative.	

Appendix 2. Summary of Findings

Study	Prevalence	Sensitivity	Specificity	Positive likelihood ratio	Negative likelihood ratio
Bar 2020	0.3	0.97 [0.83, 1.00]	0.62 [0.50, 0.74]	2.57	0.05
Dini 2020	0.6	0.79 [0.69, 0.86]	0.57 [0.43, 0.70]	1.84	0.37
Fonsi 2020	0.7	0.68 [0.52, 0.81]	0.79 [0.54, 0.94]	3.24	0.40
Narinx 2020	0.2	0.96 [0.79, 1.00]	0.59 [0.47, 0.71]	1.19	0.31
Pare 2020	0.6	0.92 [0.84, 0.97]	0.71 [0.61, 0.80]	2.03	0.20
Haak 2020	0.3	0.93 [0.68, 1.00]	0.21 [0.13, 0.32]	2.36	0.07
Peyrony 2020	0.6	0.89 [0.71, 0.98]	0.56 [0.30, 0.80]	7.09	0.26
Lieveld 2020	0.4	0.77 [0.62, 0.88]	0.89 [0.75, 0.97]	3.17	0.11

Appendix 3: Forest Plots

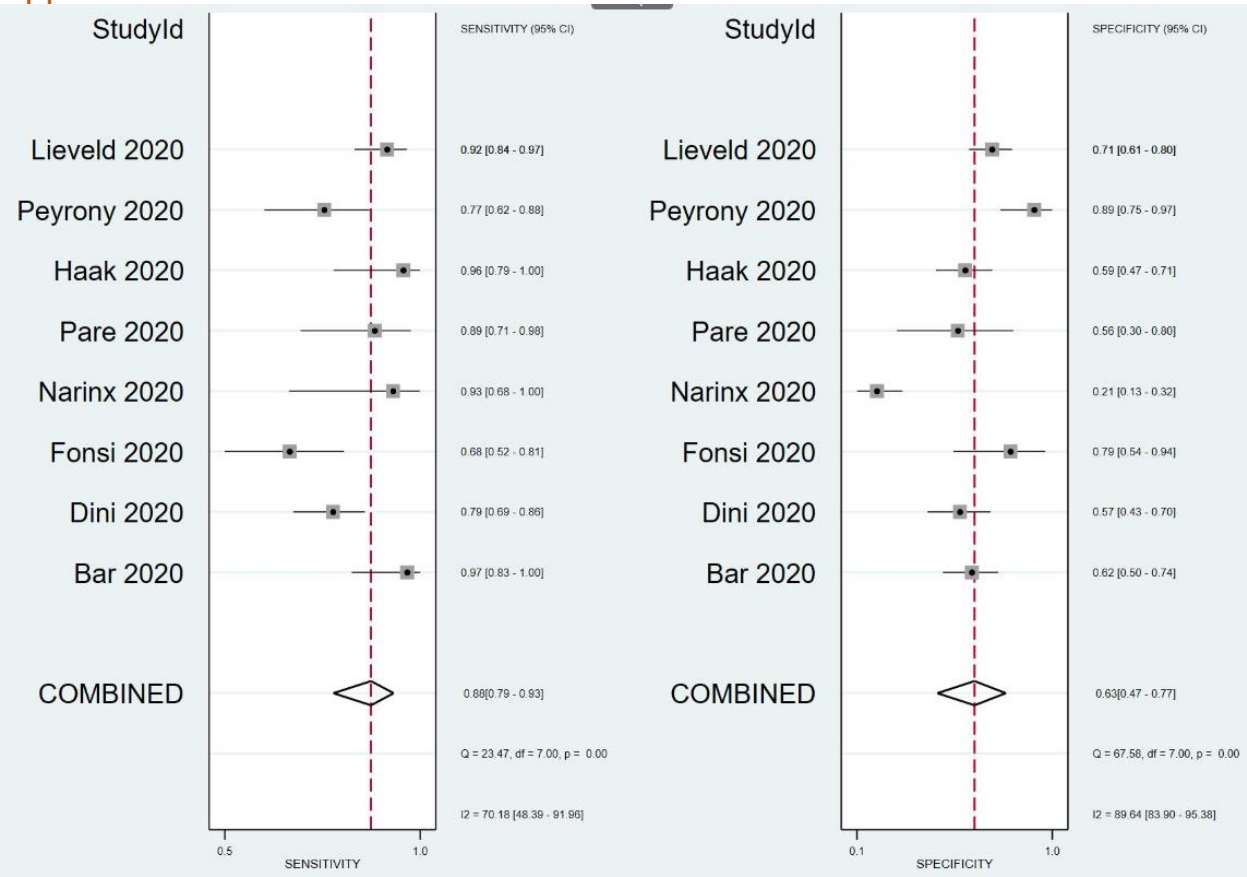

Figure 1. Forest plot of diagnostic performance of lung ultrasound compared with RT-PCR (n =8 studies)

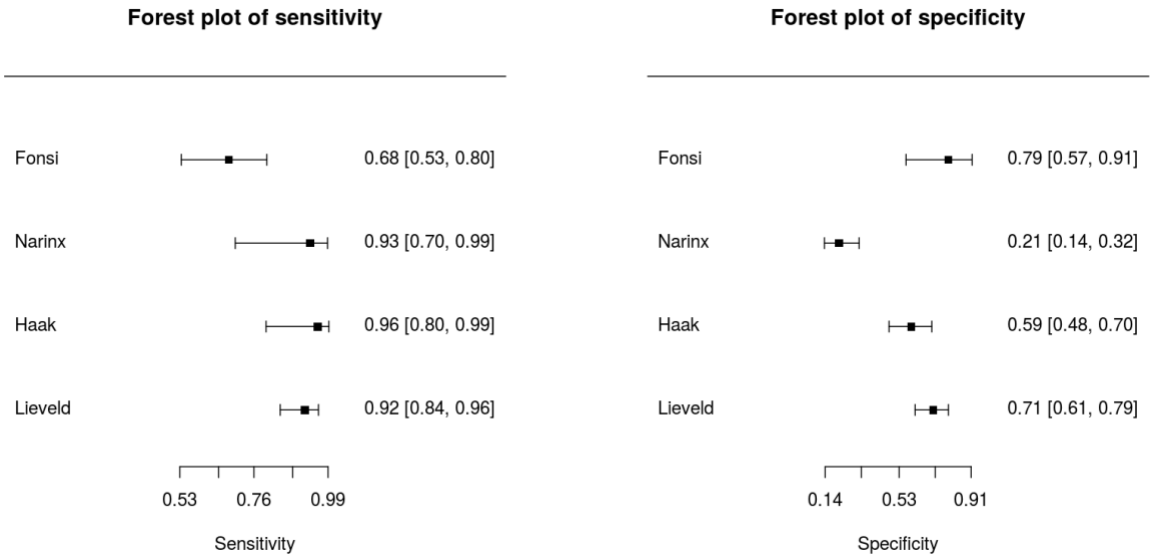

Figure 2. Pooled paired forest plots showing individual and pooled sensitivity and specificity estimates of lung ultrasound done by an experienced reader for the diagnosis of COVID-19

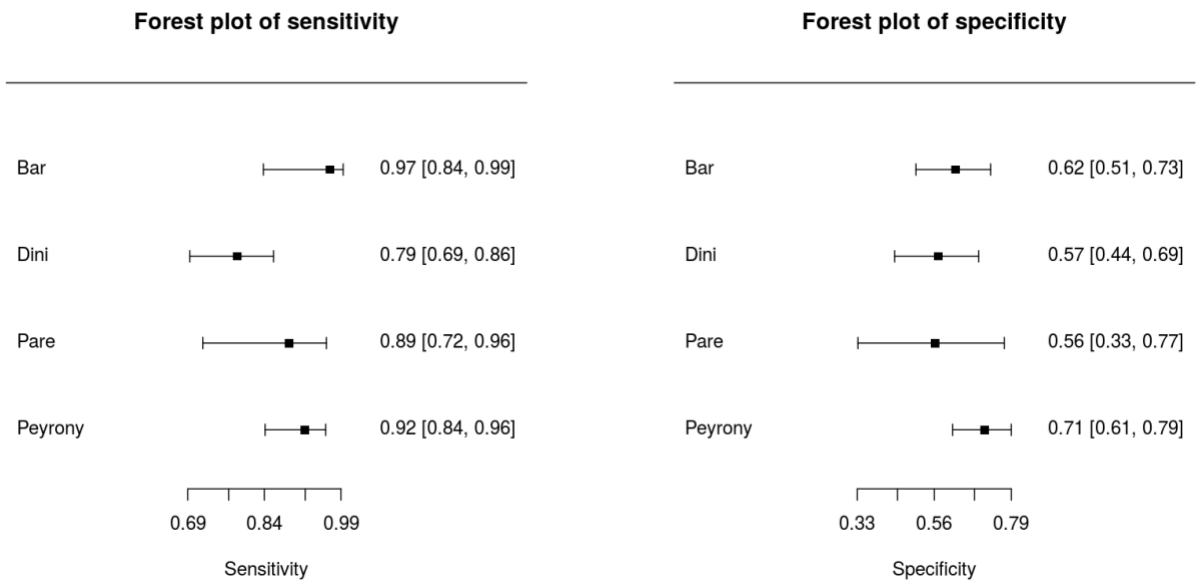

Figure 3. Pooled paired forest plots showing individual and pooled sensitivity and specificity estimates of lung ultrasound done by a reader with unclear experience for the diagnosis of COVID-19

Appendix 4: GRADE Evidence Profile

Question: Should lung ultrasound alone be used to diagnose COVID-19 in patients suspected with COVID-19?

Sensitivity	0.88 (95% CI: 0.79 to 0.93)
Specificity	0.63 (95% CI: 0.47 to 0.77)

Prevalences	1%	5%	10%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 1%	pre-test probability of 5%	pre-test probability of 10%	
True positives (patients with COVID-19)	8 studies 809 patients [a]	cross-sectional (cohort type accuracy study)	not serious	not serious	serious	not serious [b]	none	9 (8 to 9)	44 (40 to 47)	88 (79 to 93)	⨁⨁⨁◯ MODERATE
False negatives (patients incorrectly classified as not having COVID-19)								1 (1 to 2)	6 (3 to 10)	12 (7 to 21)	
True negatives (patients without COVID-19)	8 studies 809 patients [a]	cross-sectional (cohort type accuracy study)	not serious	not serious	serious	serious [c,d]	none	624 (465 to 762)	598 (446 to 731)	567 (423 to 693)	⨁⨁◯◯ LOW
False positives (patients incorrectly classified as having COVID-19)								366 (228 to 525)	352 (219 to 504)	333 (207 to 477)	

Explanations

a. Bar 2020, Dini 2020, Fonsi 2020, Hakk 2020, Lieveld 2020, Narinx 2020, Pare 2020, Peyrony 2020,

b. Inconsistency downgraded by 1 level I2 = 70.18%

c. Imprecision downgraded by one due to wide confidence interval

d. Inconsistency downgraded by 1 level I2 = 89.64%

Appendix 5: Characteristics of Ongoing Studies

NCT Number	Title	Interventions	Outcome Measures	Study Completion
NCT04351802	CORonavirus (COVID-19) Diagnostic Lung UltraSound Study	Diagnostic Test: Lung ultrasound	Diagnosis of COVID-19 on lung ultrasound, difference in diagnosis of COVID-19 on lung ultrasound vs. chest x-ray	January 20, 2021
NCT04351803	Accuracy of Lung Ultrasound in the Diagnosis of covid19 Pneumonia	Diagnostic Test: Lung ultrasound	Lung Ultrasound accuracy in rule-out of patients with respiratory symptoms (fever and / or cough and / or dyspnoea) during the SARS-CoV-2 epidemic compared to nasopharyngeal swab and a composite reference standards	May 31, 2021
NCT04351804	Screening COVID-19 by Point-of-care Lung Ultrasound: a Validation Study	Diagnostic Test: Lung ultrasound	Accuracy of diagnosis of interstitial syndrome by lung ultrasound	December 30, 2020
NCT04351805	Lung Ultrasound to Diagnose COVID-19	Diagnostic Test: COVID-19 RT-PCR|Procedure: lung ultrasound	Lung ultrasound/ biological correlation research modulating the severity of Covid-19 disease	September 28, 2021
NCT04351806	The Use of Focused Lung Ultrasound in Patients Suspected of COVID-19	Focused Lung Ultrasound	• FLUS findings and respiratory failure • FLUS findings and chest x-ray. • FLUS findings and admission to intensive care. • FLUS findings and SAR-CoV-2 PCR-test result.	May 15, 2020
NCT04351807	The Utility of Bedside Lung Ultrasonography on Diagnosis of COVID-19	Device: Bedside lung ultrasound	• Presence of viral pneumonia caused by COVID 19	September 10, 2020