The Value of Lung Ultrasound to Detect the Early Pleural and Pulmonary Pathologies in Nonhospitalized COVID-19-Suspected Cases in a Population With a Low Prevalence of COVID-19 Infection

A Prospective Study in 297 Subjects

Ehsan Safai Zadeh, MD, Katharina P. Huber, Christoph F. Dietrich, MD, Corinna Trenker, MD, Evelyn Martin, MD, Björn Beutel, MD, Birgit Wollenberg, MD, Christian Görg, MD

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Address correspondence to Dr. Ehsan Safai Zadeh, University Hospital Giessen and Marburg, Interdisciplinary Center of Ultrasound Diagnostics, Baldingerstraße, 35042 Marburg, Germany.

E-mail: ehsan_sz@yahoo.de

Abbreviations

ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; LUS, lung ultrasound; RT-PCR, reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

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Objectives—This prospective study aimed to evaluate the value of B-mode lung ultrasound (LUS) for the early diagnosis of coronavirus disease 2019 (COVID-19) infection in nonhospitalized COVID-19 suspected cases in a population with a low prevalence of disease.

Methods—From April 2020 to June 2020, in an ambulatory testing center for COVID-19-suspected cases, 297 subjects were examined by LUS before a nasopharyngeal swab was taken for a reverse transcription polymerase chain reaction (RT-PCR) test. The following LUS findings were defined as pathological ultrasound findings and were analyzed: the presence of 1) pleural effusion, 2) B-lines, 3) fragmented visceral pleura, 4) consolidation, and 5) air bronchogram in the consolidation. The LUS findings were compared with the RT-PCR test results.

Results—The result of the RT-PCR test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was positive in 11 and negative in 286 subjects, and the prevalence of COVID-19 infection in the study participants was 3.7%. On LUS, a pathological finding could be detected in 56/297 (18.9%) study participants. The LUS revealed a sensitivity of 27.3%, a specificity of 81.5%, a positive predictive value of 5.4%, a negative predictive value of 96.7%, and a diagnostic accuracy of 79.9% for the identification of COVID-19 infection.

Conclusions—For the identification of COVID-19 infection, LUS is highly sensitive to the patient spectrum and to the prevalence of the disease. Due to the low diagnostic performance in nonhospitalized COVID-19 cases in low-prevalence areas, LUS cannot be considered to be an adequate method for making a diagnosis in this group.

Key Words—COVID-19-suspected cases; low prevalence; lung ultrasound; nonhospitalized; pleural and pulmonary pathologies; SARS-CoV-2

The infectious disease coronavirus disease 2019 (COVID-19) first appeared at the end of 2019 in the Chinese metropolis of Wuhan.[1] The disease has spread worldwide at a rapid pace and has led to the overburdening of healthcare systems in many

countries. Suspected cases of COVID-19 should, if possible, be detected outside clinics in suitably equipped rooms by direct molecular biological detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using a reverse transcription polymerase chain reaction (RT-PCR) test on samples from deep throat or nasal swabs, according to the reference method published by the National Consiliary Laboratory for Coronaviruses (Charité Institute of Virology).[2] The RT-PCR test is the first method of choice and the gold standard in primary diagnostics due to its simple and rapid feasibility and low invasiveness.[3] Furthermore, the SARS-CoV-2 rapid antigen test is recommended in the WHO guidelines as a cost-effective method for detecting SARS-CoV-2 in patients with high viral loads.[4,5] However, the diagnosis of COVID is a challenge in several developing countries due to the lack of capacity for large-scale testing.[6] Furthermore, in some developing countries, the use of laboratory resources for COVID-19 testing leads to delays in identifying other diseases, such as acquired immunodeficiency syndrome.[7] Based on this knowledge, the need remains to develop new nonlaboratory-based methods, including imaging procedures, to make a diagnosis in COVID-19-suspected cases. In contrast to other imaging methods, such as computed tomography, LUS can be applied at the bedside.[8,9] In addition to immediate availability, the benefits of this procedure include easy disinfection, unlimited repeatability, low personnel and time requirements, and lack of radiation exposure.[8, 10–12]

The diagnostic performance of LUS in the diagnosis of COVID-19 has already been investigated in several studies.[13–16] However, there are limited data available regarding the diagnostic performance of LUS in the diagnosis of COVID-19 in populations with low prevalence of the disease or in nonhospitalized patients. Therefore, the findings of previously performed studies could not be generalized to nonhospitalized populations with low prevalence of COVID-19 disease. Taking into account the development of different effective vaccines, in future, the potential of LUS in nonhospitalized populations with low prevalence of disease will be increasingly relevant and should be evaluated.

The aim of this prospective study is to evaluate the value of LUS for the early diagnosis of COVID-19 infection in nonhospitalized COVID-19-suspected cases in a population with a low prevalence of disease and to compare the results with the findings of previously performed studies with moderate or high prevalence of COVID-19 infection in a hospital testing setting.

Materials and Methods

This prospective study was approved by the local ethics committee and conducted in accordance with the amended Helsinki Declaration on ethical principles for medical research involving human subjects. All study participants were informed about the study by a doctor and signed a written consent form.

The study was performed between April 2020 and June 2020 in an ambulatory COVID-19 testing center in Germany for individuals suspected of having COVID-19 in an area with a low incidence rate (defined as an area with less than 10 new cases weekly per 100,000 population).

A total of n = 297 subjects (119 men and 178 women; average age 42.2 years, range 18–84 years) participated in the study. Inclusion criteria were written informed consent to participate in the study, age over 18 years, and no pregnancy. All subjects were referred to the ambulatory COVID-19 testing center by their family doctor or local health department based on their symptoms or contact with a COVID-19 patient. Severely symptomatic patients were referred directly to the local hospital.

At the ambulatory COVID-19 testing center, a nasopharyngeal swab for RT-PCR testing was performed in all subjects.[2] An additional LUS was performed in a separate examination room for all study participants. The hygiene and infection prevention measures were performed according to the guidelines of the Robert Koch Institute (Germany) for COVID-19 patients.

Ultrasound Examination

The LUS examination was performed with a SonoSite M-Turbo® ultrasound machine, and a 5–2 MHz C60XI curved array transducer was used. All study participants were examined in an upright sitting position, according to the pulmonary ultrasound protocol for COVID-19 patients provided by the German Society for Ultrasound in Medicine (DEGUM).[17] The LUS examinations were performed horizontally to the ribs.

The ultrasound results were classified into normal and pathological findings. A normal finding was defined by the presence of A-line patterns (repetitive horizontal reverberation artifacts) and the absence of pathological ultrasound findings.[18] The following findings were defined as pathological ultrasound findings, according to the standardized LUS protocol for COVID-19 patients provided by the DEGUM[17, 19]:

1. The presence of pleural effusion.
2. The presence of B-lines (more than three per field of view).
3. The presence of fragmented visceral pleura.
4. The presence of consolidations.
5. The presence of air bronchogram in the consolidations.

All pathological LUS findings were saved as images. The LUS findings were compared with the RT-PCR results. All examinations were performed by two qualified examiners in the field of thoracic sonography under the supervision of a DEGUM Level III qualified examiner (C.G., internal medicine). The examiners were blinded at the time of the LUS examination regarding the RT-PCR results.

The LUS data were analyzed by two independent, qualified investigators (E.S., K.H.). In the event of a disagreement between the two examiners, the final decision was made by a third experienced investigator (C.G.). At the time of LUS data analysis, the investigators were blinded regarding the RT-PCR results and the clinical symptoms of the participants.

Statistical Analysis

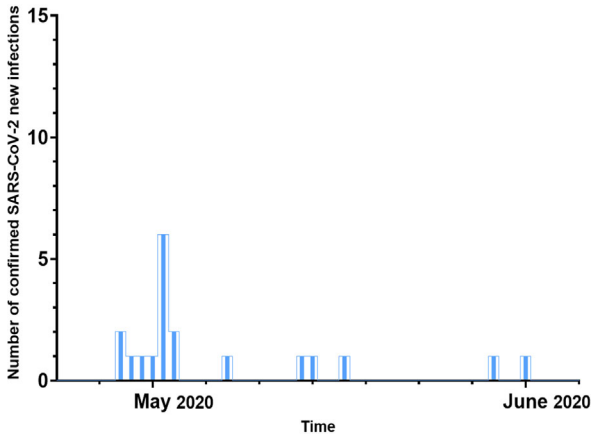
Statistical evaluation was performed on the categorical variable using Fisher's exact test and on continuous data using Mann–Whitney tests. Cohen's kappa statistics were applied to measure interrater reliability. A *P*-value of <.05 was defined as significant. In addition, sensitivity, specificity, positive and negative predictive values, and diagnostic accuracy were evaluated for the clinical and pathological ultrasound findings.

Results

Characteristics of Participants

In the entire defined study county with a population of 245,754 people, there were a total of 19 confirmed COVID-19 new infections during the study period (Figure 1).

Figure 1. Number of new infections in the defined study county with a population of 245,754 people. Nineteen new infections were confirmed during the study period in this county.



At the ambulatory testing center, 297 participants were included in the study, and the result of the RT-PCR test for SARS-CoV-2 was positive in 11 and negative in 286. The prevalence of COVID-19 infection in the study participants was 3.7%. The baseline characteristics of the study participants are presented in Table 1.

Ultrasound Findings of Participants

In total, a pathological ultrasound finding was detected in 56/297 (18.9%) study participants (Table 2). In 19/56 (33.9%) patients, a pleural effusion was observed (Figure 2A); in 27/56 (48.7%), B-lines (Figure 2B); in 25 (44.6%), a fragmented pleura (Figure 2C); in 4/56 (7.1%), a consolidation without air bronchogram (Figure 2D); and, in 2/56 (3.6%), a consolidation with air bronchogram (Figure 2E). Of the participants with a SARS-CoV-2-positive test result, a pathological finding (a fragmented pleura) was observed 3/11 (27.3%) (Figure 2C) and no pathological findings were detected in 8/11 (72.7%). Of the participants with a SARS-CoV-2-negative test result, a pathological ultrasound finding was observed in 53/286 (18.5%) and no pathological ultrasound findings were detected in 233/286 (81.5%).

For the pathological ultrasound findings, there were no significant differences between patients with a SARS-CoV-2-positive test result and those with a SARS-CoV-2-negative test result ($P = .4$, Fisher's

Table 1. Baseline Characteristics of the Study Participants

Variable	All Study Participants (n = 297)	RT-PCR-Positive Participants (n = 11)	RT-PCR-Negative Participants (n = 286)	*P*-Value
Demographic characteristic				
Age (years, mean) ± SD	42.2 ± 16.3	46.9 ± 14.1	42.1 ± 16.4	.26
Sex				
Male	119 (40.1%)	3 (27.3%)	116 (40.6%)	.54
Female	178 (59.9%)	8 (72.7%)	170 (59.4%)	
Smoking status				
Never smoked	170 (59.6%)	7 (63.6%)	171 (59.8%)	1
Smoker or former smoker	116 (40.4%)	4 (36.4%)	115 (40.2%)	

A *P*-value of <.05 was defined as significant.
RT-PCR, reverse transcription polymerase chain reaction; SD, standard deviation.

Table 2. B-Mode Lung Ultrasound Characteristics of Study Participants

Variable	All Study Participants (n = 297)	RT-PCR-Positive Participants (n = 11)	RT-PCR-Negative Participants (n = 286)	*P*-Value
Pathological ultrasound findings present	56 (18.9%)	3 (27.3%)	53 (18.5%)	.44
No pathological ultrasound findings present	241 (81.1%)	8 (72.7%)	233 (81.5%)	
Pleural effusion	18 (6.1%)	0 (0%)	18 (6.3%)	1
No pleural effusion	279 (93.9%)	11 (100%)	268 (93.7%)	
B-lines	27 (9.1%)	0 (0%)	27 (9.4%)	.6
No B-lines	270 (90.9%)	11 (100%)	268 (90.6%)	
Fragmented visceral pleura	26 (8.8%)	3 (27.3%)	23 (8.0%)	.06
No fragmented visceral pleura	271 (91.2%)	8 (72.7%)	263 (92.0%)	
Consolidation	7 (2.3%)	0 (0%)	7 (2.4%)	1
No consolidation	290 (97.7%)	11 (100%)	279 (97.6%)	
Air bronchogram	2 (0.7%)	0 (0%)	2 (0.7%)	1
No air bronchogram	295 (99.3%)	11 (100%)	284 (99.3%)	

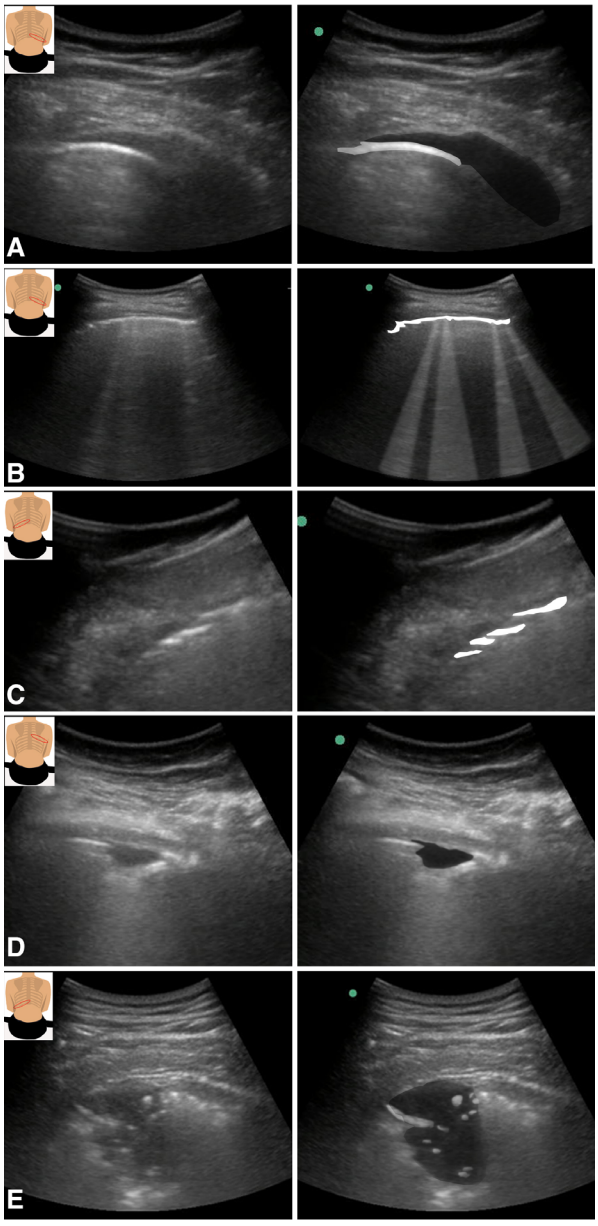
A *P*-value of <.05 was defined as significant.
RT-PCR, reverse transcription polymerase chain reaction.

exact test; Table 2). Lung B-mode ultrasound was found to have a sensitivity of 27.3%, a specificity of 81.5%, a positive predictive value of 5.4%, a negative predictive value of 96.7%, and a diagnostic accuracy of 79.9% for the identification of COVID-19 infection. The agreement between the examiners for the presence of a pathological ultrasound finding was very good (Cohen's kappa = 0.88).

Discussion

The diagnostic performance of a test is influenced by several factors such as the spectrum of patients and the sensitivity to prevalence.[20–22] The patient's spectrum of COVID-19 disease includes a broad group from asymptomatic patients to patients with acute respiratory distress syndrome (ARDS).[23] The ability of LUS to detect lung involvement depends on the severity of the disease and is lower in mild cases compared with severe case.[24,25] Furthermore, due to different demographic and clinical characteristics, a basic differentiation should be made between non-hospitalized and hospitalized COVID-19 patients.[26] Therefore, the value of LUS in identifying COVID-19 patients as a diagnostic tool must be assessed in the context of the clinical picture of patients and the testing setting. An additional important factor in the evaluation of the diagnostic performance of LUS in COVID-19 patients is the prevalence of the disease

Figure 2. Transthoracic B-mode ultrasound results. **A**, A 30-year-old female patient with a SARS-CoV-2-negative test result; a pleural effusion on the right side dorsal caudal. **B**, A 55-year-old female patient with a SARS-CoV-2-negative test result; B-lines on the right side dorsal caudal. **C**, A 46-year-old female patient with a SARS-CoV-2-positive test result; a fragmented pleura on the left side dorsal caudal. **D**, A 65-year-old female patient with a SARS-CoV-2-negative test result; a homogeneous consolidation on the right side dorsal cranial. **E**, A 27-year-old male patient with a SARS-CoV-2-negative test result; an inhomogeneous consolidation with air bronchogram on the left side dorsal caudal.



in the studied population. Colombi et al evaluated in a retrospective study the diagnostic performance of LUS in two groups with high (94%) and moderate (45%) prevalence of disease and demonstrated that the diagnostic performance of LUS was different in these two groups.[15] To date, there is limited data regarding the diagnostic performance of LUS in nonhospitalized COVID-19-suspected cases in populations with low prevalence of disease. Using a standardized approach with a qualified team of doctors, and in cooperation with the local health department, we investigated the early pathological LUS findings in nonhospitalized COVID-19-suspected cases in a population with low prevalence of disease (3.7%). During the study period, there was a lack of capacity for large-scale testing in Germany. In addition, at this time, WHO urged countries not to use immunodiagnostic tests, including the SARS-CoV-2 rapid antigen test, in clinical practice and for clinical decision-making.[27]

The presence of a pathological LUS finding was not significantly associated with a SARS-CoV-2-positive test result ($P = .44$, Fisher's exact test). Of all study subjects, 56 (18.9%) had pathological ultrasound findings. However, only 3 of 11 subjects with a SARS-CoV-2-positive test result had a pathological ultrasound finding. The sensitivity and specificity of the LUS for the identification of nonhospitalized COVID-19 patients were 27.3 and 81.5%, respectively. This illustrates the low sensitivity of LUS in nonhospitalized COVID-19 populations with low prevalence of disease compared with those with moderate or high prevalence of disease in a hospital setting regarding the diagnosis of a COVID-19 infection in previous studies (Table 3).[13–16] The sensitivity and specificity of a diagnostic test are not affected by disease prevalence.[21] The lower sensitivity of LUS in this study may be influenced by the clinical characteristics of the nonhospitalized COVID-19 patients. This indicates the high sensitivity of LUS to the spectrum of the disease.[21] In this study, LUS showed a low positive predictive value of only 5.4% for the identification of COVID-19 patients. The very low positive predictive value in this study compared with studies with higher prevalence[13–15] demonstrates the high sensitivity of LUS to prevalence of disease for the identification of COVID-19 patients (Table 3).[21]

Table 3. Diagnostic Efficiency of Pathological Ultrasound Findings for the Identification of COVID-19 Infection Depending on Testing Setting and Prevalence of Disease

Author	Prevalence of Disease (%)	Cases	Study Design	Testing Setting	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Colombi et al[15]	94.0	247	Retrospective	Hospital	94.0	7.0	94.0	7.0
Sorlini et al[16]	74.7	384	Retrospective	Hospital	92.0	64.9	88.6	73.3
Volpicelli et al[14]	69.8	1462	Prospective	Hospital	90.2	52.5	81.5	69.8
Colombi et al[15]	45.0	239	Retrospective	Hospital	93.0	31.0	52.0	83.0
Gutsche et al[13]	19.7	76	Retrospective	Hospital	93.3	55.7	34.2	97.1
Present study	3.7	297	Prospective	Ambulatory testing center	27.3	81.5	5.4	96.7

NPV, negative predictive value; PPV, positive predictive value.

Furthermore, in this study, 18.5% of patients with a SARS-CoV-2-negative test result had pathological ultrasound findings. This result indicates the nonspecificity of LUS patterns in the diagnosis of COVID-19 cases. These LUS patterns of COVID-19 disease may also be present in many cases with other respiratory diseases, including bacterial pneumonia, viral pneumonia, ARDS, and cardiogenic pulmonary edema.[28,29]

The findings of this study demonstrate the high sensitivity of LUS to the spectrum and prevalence of the disease as a diagnostic tool in identifying patients with COVID-19 infection. Furthermore, the nonspecificity of the LUS patterns of COVID-19 patients was revealed. In addition, it was found that in 18.5% of cases with negative test results, LUS patterns similar to those in patients with COVID-19 infections were present, which would support the nonspecificity of LUS in the diagnosis of COVID-19.

This study had several limitations. The definition of COVID-19 LUS patterns and the spectrum of disease vary in different studies; therefore, only a limited comparison of the studies was possible. Ultrasound examination is dynamic and highly dependent on the examiner; therefore, the possibility of examiner subjectivity could not be excluded. Furthermore, it should be considered that the nasopharyngeal swab has limited sensitivity, and patients could be mistakenly classified as SARS-CoV-2-negative.

In summary, LUS is highly sensitive to the spectrum of patients and to the prevalence of the disease for the identification of patients with COVID-19 infection. For using LUS as a diagnostic tool to identify patients with COVID-19 infection, clinicians should be directed to the findings from studies in populations with similar prevalence and spectrum of disease as those of their own areas. Due to the low diagnostic performance in nonhospitalized COVID-19 cases in low-prevalence areas, LUS cannot be considered to be an adequate method for making a diagnosis in these patients. Essentially, due to the nonspecificity of LUS findings, LUS may not be a valid method for the diagnosis of COVID-19 infection.

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[Correction added on 11 September 2021, after first online publication: Projekt Deal funding statement has been added.]

References

1. Wu F, Zhao S, Yu B, et al. A new coronavirus associated with human respiratory disease in China. *Nature* 2020; 579:265–269. https://doi.org/10.1038/s41586-020-2008-3.
2. Corman VM, Landt O, Kaiser M, et al. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. *Eurosurveillance* 2020; 25. https://doi.org/10.2807/1560-7917.es.2020.25.3.2000045.
3. Ortiz-Prado E, Simbaña-Rivera K, Gómez-Barreno L, et al. Clinical, molecular, and epidemiological characterization of the SARS-CoV-2 virus and the coronavirus disease 2019 (COVID-19), a comprehensive literature review. *Diagn Microbiol Infect Dis* 2020; 98:115094–115094. https://doi.org/10.1016/j.diagmicrobio.2020.115094.
4. Peeling RW, Olliaro PL, Boeras DI, Fongwen N. Scaling up COVID-19 rapid antigen tests: promises and challenges. *Lancet Infect Dis* 2021; 21:e290–e295. https://doi.org/10.1016/s1473-3099(21)00048-7.

5. World Health Organization Antigen-detection in the diagnosis of SARS-CoV-2 infection using rapid immunoassays: interim guidance. 2020. https://apps.who.int/iris/handle/10665/334253. Accessed September 2020.
6. Kobia F, Gitaka J. COVID-19: are Africa's diagnostic challenges blunting response effectiveness? *AAS Open Res* 2020; 3:4. https://doi.org/10.12688/aasopenres.13061.1.
7. Lagat H, Sharma M, Kariithi E, et al. Impact of the COVID-19 pandemic on HIV testing and assisted partner notification services, Western Kenya. *AIDS Behav* 2020; 24:3010–3013. https://doi.org/10.1007/s10461-020-02938-7.
8. Dietrich CF, Mathis G, Cui XW, Ignee A, Hocke M, Hirche TO. Ultrasound of the pleurae and lungs. *Ultrasound Med Biol* 2015; 41:351–365. https://doi.org/10.1016/j.ultrasmedbio.2014.10.002.
9. Moore CL, Copel JA. Point-of-care ultrasonography. *N Engl J Med* 2011; 364:749–757. https://doi.org/10.1056/NEJMra0909487.
10. Soldati G, Demi M, Smargiassi A, Inchingolo R, Demi L. The role of ultrasound lung artifacts in the diagnosis of respiratory diseases. *Expert Rev Respir Med* 2019; 13:163–172. https://doi.org/10.1080/17476348.2019.1565997.
11. Peng QY, Wang XT, Zhang LN. Findings of lung ultrasonography of novel corona virus pneumonia during the 2019-2020 epidemic. *Intensive Care Med* 2020; 46:849–850. https://doi.org/10.1007/s00134-020-05996-6.
12. Safai Zadeh E, Weide J, Dietrich CF, Trenker C, Koczulla AR, Görg C. Diagnostic accuracy of B-mode- and contrast-enhanced ultrasound in differentiating malignant from benign pleural effusions. *Diagnostics* 2021; 11:1293. https://doi.org/10.3390/diagnostics11071293.
13. Gutsche H, Lesser TG, Wolfram F, Doenst T. Significance of lung ultrasound in patients with suspected COVID-19 infection at hospital admission. *Diagnostics* 2021; 11:921. https://doi.org/10.3390/diagnostics11060921.
14. Volpicelli G, Gargani L, Perlini S, et al. Lung ultrasound for the early diagnosis of COVID-19 pneumonia: an international multicenter study. *Intensive Care Med* 2021; 47:444–454. https://doi.org/10.1007/s00134-021-06373-7.
15. Colombi D, Petrini M, Maffi G, et al. Comparison of admission chest computed tomography and lung ultrasound performance for diagnosis of COVID-19 pneumonia in populations with different disease prevalence. *Eur J Radiol* 2020; 133:109344. https://doi.org/10.1016/j.ejrad.2020.109344.
16. Sorlini C, Femia M, Nattino G, et al. The role of lung ultrasound as a frontline diagnostic tool in the era of COVID-19 outbreak. *Intern Emerg Med* 2021; 16:749–756. https://doi.org/10.1007/s11739-020-02524-8.
17. Stock K, Matthis G & Horn R et al. Vorschlag eines standardisierten Lungen-Ultraschallprotokolls in den Zeiten von COVID-19. https://www.degum.de/fileadmin/dokumente/service/Downloads/Poster_A4-Lungenultraschall-Protokoll_DEGUM_SGUM_OEGM_V3_06042020_Print_digital_NEU.pdf. Accessed April 2020.
18. Koenig SJ, Narasimhan M, Mayo PH. Thoracic ultrasonography for the pulmonary specialist. *Chest* 2011; 140:1332–1341. https://doi.org/10.1378/chest.11-0348.
19. Safai Zadeh E, Beutel B, Dietrich CF, et al. Perfusion patterns of peripheral pulmonary lesions in COVID-19 patients using contrast-enhanced ultrasound (CEUS). *J Ultrasound Med* 2021. https://doi.org/10.1002/jum.15624.
20. Melbye H, Straume B. The spectrum of patients strongly influences the usefulness of diagnostic tests for pneumonia. *Scand J Prim Health Care* 1993; 11:241–246. https://doi.org/10.3109/02813439308994838.
21. Šimundić A-M. Measures of diagnostic accuracy: basic definitions. *EJIFCC* 2009; 19:203–211.
22. Ransohoff DF, Feinstein AR. Problems of spectrum and bias in evaluating the efficacy of diagnostic tests. *N Engl J Med* 1978; 299:926–930. https://doi.org/10.1056/nejm197810262991705.
23. Zeng H, Ma Y, Zhou Z, et al. Spectrum and clinical characteristics of symptomatic and asymptomatic coronavirus disease 2019 (COVID-19) with and without pneumonia. *Front Med* 2021; 8:229. https://doi.org/10.3389/fmed.2021.645651.
24. Lu W, Zhang S, Chen B, et al. A clinical study of noninvasive assessment of lung lesions in patients with coronavirus disease-19 (COVID-19) by bedside ultrasound. *Eur J Ultrasound* 2020; 41:300–307. https://doi.org/10.1055/a-1154-8795.
25. Campagnano S, Angelini F, Fonsi GB, Novelli S, Drudi FM. Diagnostic imaging in COVID-19 pneumonia: a literature review. *J Ultrasound* 2021; 15:1–13. https://doi.org/10.1007/s40477-021-00559-x.
26. Bergquist SH, Partin C, Roberts DL, et al. Nonhospitalized adults with COVID-19 differ noticeably from hospitalized adults in their demographic, clinical, and social characteristics. *SN Compr Clin Med* 2020; 2:1349–1357. https://doi.org/10.1007/s42399-020-00453-3.
27. WHO Advice on the use of point-of-care immunodiagnostic tests for COVID-19. https://www.who.int/news-room/commentaries/detail/advice-on-the-use-of-point-of-care-immunodiagnostic-tests-for-covid-19. Accessed April 2020.
28. Gargani L, Soliman-Aboumarie H, Volpicelli G, Corradi F, Pastore MC, Cameli M. Why, when, and how to use lung ultrasound during the COVID-19 pandemic: enthusiasm and caution. *Eur Heart J Cardiovasc Imaging* 2020; 21:941–948. https://doi.org/10.1093/ehjci/jeaa163.
29. Kharasch S, Duggan NM, Cohen AR, Shokoohi H. lung ultrasound in children with respiratory tract infections: viral, bacterial or COVID-19? A narrative review. *Open Access Emerg Med* 2020; 12:275–285. https://doi.org/10.2147/oaem.s238702.