Benefits, Open questions and Challenges of the use of Ultrasound in the COVID-19 pandemic era. The views of a panel of worldwide international experts

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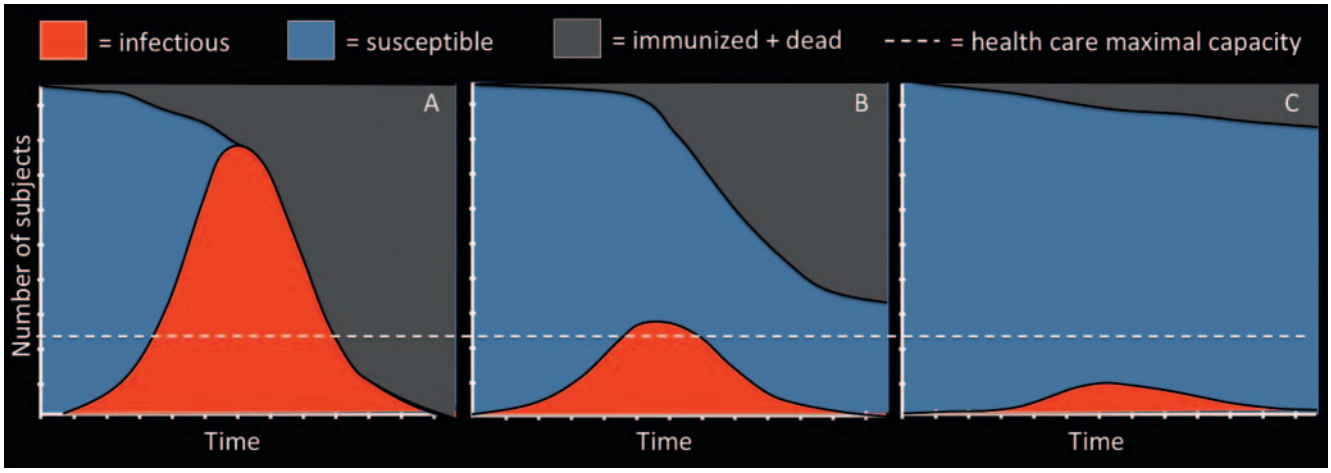
In the very last days of the year 2019a new virus of the coronavirus family, named Sars-Cov-2 [1] was identified as responsible for the outbreak of cases of human pneumonia in Wuhan, China, a condition named Corona Virus Disease of 2019 (COVID-19). This virus displayed a rapid worldwide spread, with rates significantly higher and with much more severe clinical manifestations than those of seasonal influenza virus. From the initial source in China the virus has progressively spread also to Europe, starting to heavily impact Northern Italy, and later to other European countries and the United States, which by the end of March 2020 has become the country with the largest number of documented cases. Since the virus is new and highly infectious, all humans are potentially susceptible. Moreover, the outbreak took place unexpectedly and in a densely populated Chinese city causing a rapid exponential growth in the number of cases. This led to a huge influx of patients to medical facilities demanding investigation and support for persisting high fever and respiratory compromise. Depending on the local population reaction and the rapidity of local authorities response in combating an infectious diffusive public health threat, different modalities of this epidemic can take place (https://www.youtube.com/watch?v=gxAaO2rsdIs) (▶ **Fig. 1**). Unfortunately, not only in China, but also in Northern Italy, Spain, France and America, just to name some most hit countries, authority reaction and population restrictions were not sufficiently timely to avoid the exponential growth, producing a burst of cases. This has inevitably resulted in overwhelming the capacity of the healthcare systems, in particular hospital provision, and the ability to properly allocate patients to the appropriate clinical units. This has led, particularly in North Italy and Spain, to the risk of collapse of normally comprehensive and excellent health care systems. The sheer volume of sick patients has overrun the capability of the hospitals to provide the expected healthcare, creating a sort of war scenario.

With no specific disease treatment existing, there are several requirements to try to limit the spread of the infection. There must be early identification of infectious cases, with rapid laboratory testing, ideally with an accurate rapid clinical diagnosis to isolate the positive subjects, preventing further spread of the infection. There should be appropriate triage of positive patients into those who can remain safely at home and those that require hospital admission. It would also be important to predict early any deterioration in order to timely upscaling of the intensity of care (whenever possible) and furthermore, there is need for optimal patient management during respiratory failure and in the intensive care unit stay. The transmission of this easily spreading infection during patient care has also to be avoided.

Since COVID-19 is primarily a respiratory disease [2] the expectation would be that lung imaging would be essential for the diagnosis [3].

Computed tomography (CT) imaging has been reported to be a highly sensitive technique in identifying findings suggestive of COVID-19 pulmonary involvement, which includes bilateral “subpleural and lower lobe located ground glass” abnormality [4]. Nonetheless, any opacity at CT has low specificity, as these appearances are caused by other viral infections [5]. These good sensitivity and positive predictive values are therefore valid only in the setting of an epidemic COVID-19, when there is a very high “a priori” probability of COVID-19 in the presence of respiratory symptoms. However, even under these conditions the capa-



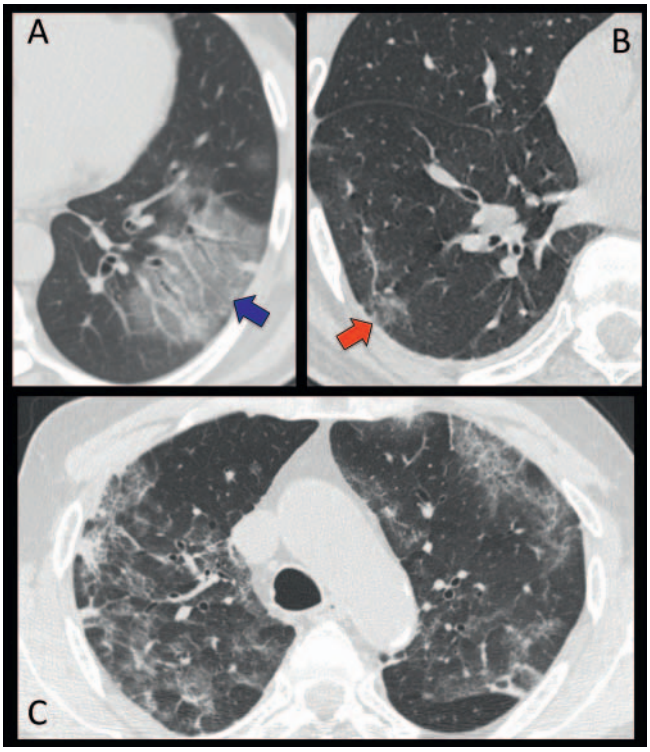
▶ **Fig. 1** Examples of spread of infectious disease under different counteracting measures and burden on the health care system. Panel A = no measure is taken. The agent spreads very fast, making susceptible subjects to disappear and be replaced by dead or immune subjects. During the peak of infected subjects the demand of assistance largely passes the capacity of the health care system to react (dashed white line) and potentially leading to a collapse of healthcare. Panel B = counteracting measures are taken, but not rapidly and intensely enough to avoid the peak of infected subjects passing the capacity of the healthcare system to react. Management of patients out of the best standard of care is necessarily adopted. Panel C: counteracting measures are taken strict and timely enough to avoid the peak of infected subjects to pass the capacity of reaction of the healthcare system, which is able to maintain the best standard of care for everyone.

city of CT to rule out COVID-19 in the presence of negative pulmonary findings is far from sufficient [6, 7].

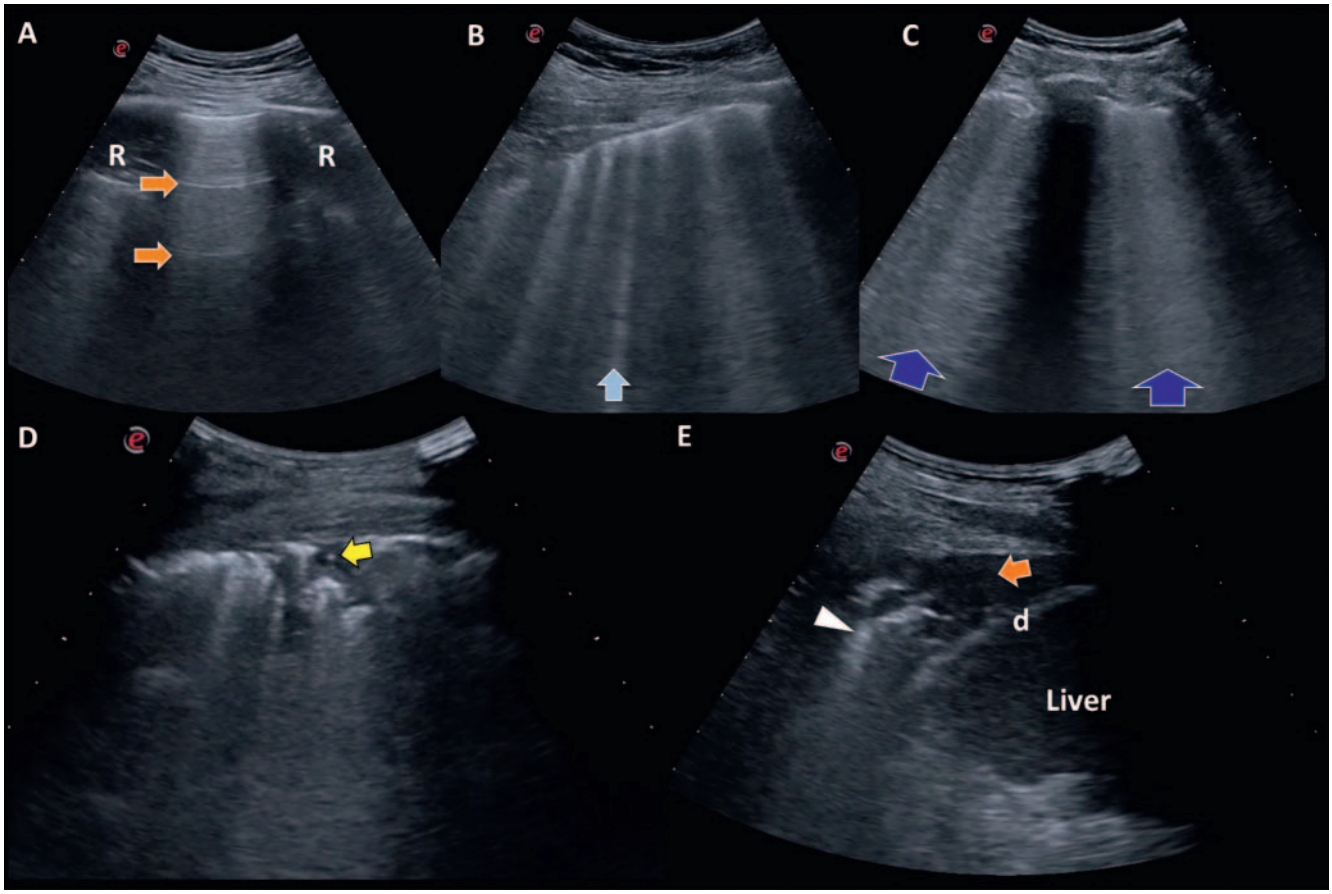
Against this background, a panel of internation experts has taken the opportunity to evaluate the position of ultrasound (US) in the management of COVID-19, in order to summarize for our journal readers, an outlook of the benefits, but also open questions and challenges of the use of US in the setting of COVID-19 epidemic [8].

Typically, the COVID-19 pulmonary involvement initially affects the declivous areas, corresponding to the superficial areas of the lungs, usually in the posterior basal regions (▶ **Fig. 2**) [4], probably because sick patients tend to sit or lie in bed for most of the time. Fortunately, these areas are explorable with chest US and these areas of abnormality were shown to be possibly detected also early in the course of the disease, as shown by Su et al in this issue of the journal [8]. The pulmonary involvement may then become extensive with the progression not only of the local severity of the disease, but spreading to involve the entire lung fields bilaterally. At the most severe stage, US is nearly invariably able to detect the pulmonary involvement, but the sensitivity of US in the early phase has not yet been definitively elucidated (▶ **Fig. 2**).

Typical patterns of the COVID-19 pulmonary involvement are the appearance of multiple B-lines, with heterogeneous involvement of the lungs (mixing A and B patterns nearby, in a different manner from cardiac pulmonary edema, which shows homogeneous increase in B lines), appearance of thickened and irregular pleural contour line, onset of small superficial consolidations and in more severe cases large areas of consolidation with air bronchograms and also minimal or rarely larger pleural space fluid effusions (▶ **Fig. 3**). However, since the role of CT in COVID-19 is still questioned [6], that of US is not unexpectedly even more debated and uncertain.



▶ **Fig. 2** Examples of CT appearance of the pulmonary involvement by COVID-19. Panel A = moderate left lung posterodorsal ground glass opacity. Panel B = Mild right lung postero basal subpleural infiltrate. Panel C = extensive bilateral diffuse lung alterations with ground glass appearance, perilobular thickening and small consolidations.



▶ **Fig. 3** Illustrations of lung US patterns in COVID-19. **A**) normal A pattern in longitudinal scan (green arrows indicate A lines). R = rib shadowing; **B**) black and white or **A/B** pattern in a scan along the intercostal space (increased number of B lines, light blue arrow indicates one B line); **C**) coalescent B lines (indicated by the blu arrows) or «white lung» pattern; **D**) jagged/scarred pleural line with an emerging small consolidation (yellow arrow); **E**) more prominent basal consolidation of the right lung (orange arrow) with hyperechoic air bronchogram (white arrowhead). d = diaphragm.

We would like therefore to suggest a list of potential benefits of US and raise some unanswered clinical questions in this setting:

1) Ultrasound can detect signs of pulmonary involvement [8]. Findings of pulmonary interstitial syndrome (± with consolidations) associated with fever, absolute lymphopenia and variable increase in LDH, ferritin, C-reactive protein and Interleukin-6 [9] are extremely suggestive of COVID-19 in an epidemic setting such as the current situation. Whether or not additional testing, such as throat/nasal swab for RNA testing [10] and/or chest plain X-ray and/or CT imaging remain absolutely and immediately mandatory or alternatively patients can be directly allocated to COVID-19 wards has to remain a decision based on the local and continuously changing circumstances. Crowding of patient at first aid /emergency facilities, time to obtain results of swab RNA testing [10] and chest CT imaging, often taking some hours, particularly when demand is high, have to be taken into consideration.

To correctly establish the appropriate use of US in the diagnostic triage of COVID-19, there is a lack of relevant scientific information. Important aspects that are needed include the sensitivity of the US technique for different degrees of pulmonary involvement (Su et al report on a limited number of cases) [8], the positive predictive value either in a setting of COVID-19 endemic disease or under normal conditions, the negative predictive value for mild, moderate and severe involvement. Briefly, despite some benefits of US, its role in clinical decision-making when imaging the individual suspected case is yet to be established.

2) Whether US can be utilized and is cost/effective in detecting the progression (or regression) of the severity of lung involvement over the days, with either in- or out-patients (in other words the capacity to distinguish mild, moderate and severe involvement) is still to be adequately investigated and clarified. A positive answer to this question would bring US into possible use in patient monitoring, potentially integrating with the chest X-ray or CT.

3) There is a potential benefit from the use of US in intensive care units to assess the effect of clinical maneuvers, such as bronchoscopy, aiming at restoring bronchial patency, following an US detection of poorly ventilated large consolidations. Ultrasound can additionally detect pneumothorax, which occurs either spontaneously or favored by pulmonary regions of hyper-insufflation in ventilated patients. Whether US could also be utilized at the bedside to screen for patients who could be candidates that would perhaps benefit from non-invasive ventilation or from lying in prone position, also deserves investigation (e. g. extensive consolidations of the posterior regions, especially without bronchograms would not suggest any benefit in placing patients in a prone position; conversely consolidations with extensive air

bronchograms are pulmonary regions likely to be recruited by increasing ventilation pressure). Basal lung US was not able to predict oxygenation response to the prone position in non COVID-19 acute respiratory distress syndrome, but was instead predictive of improved aeration gain in the anterior areas [11].

4) Ultrasound is very useful to guide pleural punctures for safer fluid drainage and for the assessment of the changes in the amount of pleural fluid, which is an established practice, although pleural effusions are not a typical feature of COVID-19.

5) There is clear scope for the US assessment of the heart and vena cava, particularly when COVID-19 might be combined with cardiovascular comorbidities. Ultrasound may guide the amount of intravenous fluids to be infused (obviously less recommended in wet lungs and in overdistended vena cava) and assess left and right ventricular function in case of suspicion of cardiac failure. Such assessments may also be performed adequately with pocket size scanners [12].

6) Portable US scanners can also be transported easily to the home of patients with fever and mild symptoms or to mobile triage checkpoints for such patients to search for signs of pulmonary involvement. In this way, US could provide additional information beside pulmonary auscultation and oxygen saturation (with a finger pulse-oximeter), which are the only home or mobile checkpoint visit tools presently available for respiration investigation. However, the real cost or effectiveness of such a strategy is speculated.

7) Ultrasound has the potential in the future to be operated remotely, with mechanical arms moving the transducer on the patient who lies isolated in protected rooms, limiting the risk of viral transmission.

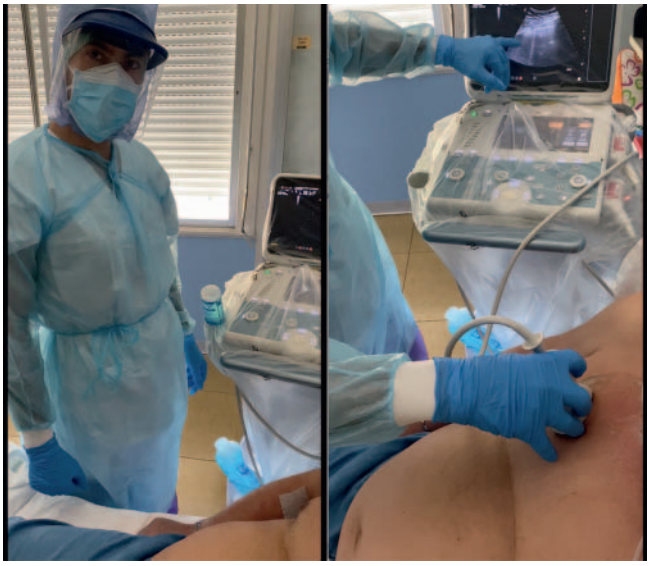
8) A urgent need is felt of worldwide standardization of reporting modalities in lung US and especially in COVID-19 [13].

Despite the wide availability of US, its low cost, portability, patient acceptability, and ease of use in the poorly cooperative patients, in comparison to a CT or X-ray, there are a number of serious challenges in the use of US in the setting of COVID-19.

1) There is a prolonged exposure of US operators to patients and vice versa, longer and closer than with CT examinations, which can increase the risk of coronavirus transmission. Therefore, when scanning COVID-19 positive patients (or patients at high risk of being COVID-19 positive) US operators should wear adequate personal protective equipment (PPE), including FFP2 = N95 or FFP3 faces masks, gloves, disposable caps and shoe covers and protective glasses or goggles or face barriers (▶ **Fig. 4**). This equipment aims to protect operators from potentially infectious patients, but also to protect patients with unconfirmed suspicion upon COVID-19 from receiving COVID-19 from asymptomatic and unaware health care operators.

2) Ultrasound scanner boards are not designed to be cleaned with liquid disinfectants, liquids will almost invariably saturate the keyboard or the command buttons. New US scanners should take into consideration these aspects, namely the resistance to disinfectants and the ease to clean and disinfect the main body of the equipment.

3) Modalities of disinfection of transducers have been inadequately optimized and are unknown to many operators. Under normal conditions a cleaning tissue to wipe the transducers might be sufficient. However, with the increase in hazardous transmittable infections (e. g. SARS-CoV-2, carbapenemase-producing enterobacteriaceae, methicillin resistant staphylococcus, etc.) more research should be devoted to verify the most convenient and accessible method of disinfection that is useful in actual daily practice. Most manufacturers and scientific societies tend to suggest procedures such as immersion of the transducer in a disinfectant solution for 1–5 minutes or alternatively, in a stronger disinfectant solution for at least 30 seconds. However, such measures are felt to be complex, making adherence difficult [14, 15]. Moreover, and importantly, immersion of transducers in potent disinfectant may damage some transducers after as few as 50–100 disinfecting cycles, making such procedures impracticable. Hence disinfecting procedures should be of minimal complexity, but also preserving patient and transducer safety.



▶ **Fig. 4** Ultrasound of COVID-19 infected patients demands extensive use of Personal Protective Equipment (PPE) and possibly protection of Ultrasound equipment in the hypothesis they should be moved out of the "dirty, COVID-19 +ve" rooms, but can be carried out at the bedside, avoiding to move COVID-19 +ve patients to hospital rooms utilized by COVID-19 negative subjects.

4) The ability to maintain the US scanner protected from contamination within a COVID positive environment is not standardized. An US scanner may be entirely covered with transparent, thin and disposable nylon bags (▶ **Fig. 4**), but attention must be paid to avoid any potential overheating of the scanners. Reasonably, only the screen and the board could be covered. If no protective cover is used, it is difficult to be assured that every portion of the scanner is disinfected, should the scanner be moved outside a COVID-19 environment. Ideally each COVID-19 ward should have an US machine permanently in the ward area.

5) The interoperator reproducibility of lung US in the assessment of COVID-19 pulmonary involvement and of its severity has obviously not been tested for ethical reasons (in order not to expose two operators to the risk of becoming infected). Even though lung US is relatively easy to learn, in the hands of non-expert operators the reproducibility might be even lower.

Finally, and most importantly, every imaging procedure must be deemed essential for the ongoing clinical management of the patient, and for any US examination this is of paramount importance (not just lung US, but rather thyroid, carotid artery, liver, renal or any other examinations), as the US examination constitutes an infection risk. Ultrasound, like any other procedure performed on patients in isolation, can reduce the effectiveness of the isolation itself. Since COVID-19 individual infection is expected to last no longer than 2 to 6 weeks after symptomatic recovery, any US examination that can presumably be safely postponed by 6–8 weeks must not be performed in patients with COVID-19 active infection. Similarly, the exposure of healthcare personnel should be limited to only the essential operations in order to prevent their contagion.

Conflict of Interest

Fabio Piscaglia: Bayer, ESAOTE, La Force Guerbet , GE Healthcare, Bracco, Siemens Healthineers; **Federico Stefanini**: None; **Vito Cantisani**: Bracco, Samsung, Canon; **Paul Sidhu**: Bracco, Siemens Healtineers, Samsung, Hitachi, GE Healthcare, Philips, ITREAS; **Richard Barr**: Philips, Mindray, Siemens, Canon, Bracco, Hologic, Samsung; **Annalisa Berzigotti**: none; **Maria Cristina Chammas**: none; **Jean-Michel Correas**: Canon MS, Hitachi MS, Philips Ultrasound, Siemens Ultrasound, Supersonic Imagine; **Christopher Frank Dietrich**: Bracco, Hitachi, Pentax, Siemens Healthcare, Mindray, Supersonic, Jazz, Youkey; **Steven Feintstein**: Bracco, DIA-Imaging, GE Healthcare; **Pintong Huang**: Bracco, Philips, Mindray; **Christan Jenssen**: FALK Foundation, Hitachi, Canon, Bracco and GE; **Yuko Kono**: Bracco, Lantheus, GE, Canon; **Masatoshi Kudo**: Bayer, Eisai, GE Healthcare; **Ping Liang**: None; **Andrej Lyshchik**: GE Healthcare, Bracco Diagnostics, Siemens Healthineers, Canon Medical Systems, Elsevier; **Christian Nolsoe**: None; **Xyaoyan Xie**: None; **Francesco Tovoli**: Bayer

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