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# Association of Lung Ultrasound Score with Mortality and Severity of COVID-19: A Meta-Analysis and Trial Sequential Analysis

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## ABSTRACT

**Objectives:** The coronavirus disease 2019 (COVID-19) pandemic has rapidly spread all over the world. Lung ultrasound (LUS) has emerged as a useful tool for diagnosing many respiratory diseases. The prognostic role of LUS in COVID-19 patients has not yet been established.

**Methods:** Several databases were searched on 09 April 2021. The difference in LUS score between the death and survival groups, and the relationship between LUS score and COVID-19 severity were both assessed.

**Results:** The LUS score was significantly higher in the death group compared with the survival group (weighted mean difference (WMD) = 8.21, 95% CI: 4.74–11.67,  $P < 0.001$ ), which was confirmed by trial sequential analysis. Those with mild/moderate, severe and critical COVID-19 had a progressively higher LUS score (critical vs. severe: WMD = 8.78, 95% CI: 4.17–13.38;  $P < 0.001$ ; critical vs. mild/moderate/severe: WMD = 10.00, 95% CI: 6.83–13.17,  $P < 0.001$ ; severe vs. moderate: WMD = 5.96, 95% CI: 3.48–8.44,  $P < 0.001$ ; severe vs. mild/moderate: WMD = 7.31, 95% CI: 4.45–10.17,  $P < 0.001$ ).

**Conclusions:** The LUS score was associated with mortality and severity of COVID-19. The LUS score might be a risk stratification tool for COVID-19 patients.

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## Introduction

Global coronavirus disease-19 (COVID-19) broke out at the end of 2019 (Zhu et al., 2020). COVID-19 has rapidly spread all over the world, causing a pandemic within a short period due to its transmission dynamics. By the end of January 2021, more than one hundred million COVID-19 cases were confirmed in 215 countries, causing just under two million deaths (Bajaba et al., 2021).

The clinical manifestation spectrum of infection with COVID-19 ranges from mild self-limited disease to severe pneumonia (Hatmi, 2021). The mortality rate differs by countries and the infection rate is still rising, around 1%–5% (Kwok et al., 2021). However, the patients who are required to be transferred to intensive care units (ICU) have suffered from a very high mortality rate (45%) (Brandao Neto et al., 2021).

Since polymerase chain reaction analysis became the gold standard for diagnosing COVID-19, doctors devoted more time and ef-

fort to the studies regarding risk stratification or prediction about COVID-19. Recent studies have revealed that early prediction might assist clinicians in stratifying risk and initiate early therapy for patients with serious conditions (Gong et al., 2020). However, due to the serious economic burden caused by the COVID-19 pandemic, there is a critical need for a low-cost tool to stratify risk.

In recent decades, lung ultrasound (LUS) has emerged as a useful and non-invasive tool for both adult and pediatric patients, enabling rapid evaluation of many chest conditions. This popularity is due to several advantages of the method such as low cost, rapidity, lack of ionizing radiation, availability at the bedside, and repeatability of the method (Iovine et al., 2021). LUS can be performed for: diagnosis and follow-up of pediatric lung infectious diseases (namely bronchiolitis and pneumonia) and lung complications (such as pneumothorax, pleural effusion and lung abscess); diagnosis of respiratory distress syndrome (Ma et al., 2020); diagnosis and follow-up of pulmonary edema; diagnosis of thoracic trauma and early detection of signs of child abuse (Iovine et al., 2021); diagnosis of pneumothorax (Fei et al., 2021); and assessing and predicting acute heart failure (Johannessen et al., 2021). LUS has become part of the basic knowledge of physicians caring

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for critically ill patients in emergency units and ICUs (Mayo et al., 2019; Mojoli et al., 2019).

After COVID-19 broke out, the use of LUS became common practice. In the first half of 2020, most studies focused on LUS diagnostic capacity, while few evaluated its prognostic value (Kameda et al., 2021). Some studies used the LUS score to predict the mortality of COVID-19 patients (Bosso et al., 2020). Others found that the LUS score may correlate with the severity of COVID-19 (Giorno et al., 2020). However, the results have been inconsistent, and small sample sizes can affect the strength of previous evidence. Therefore, this meta-analysis of studies was conducted with the aim of providing a more comprehensive summary of currently available research to explore the association of LUS score with mortality and severity of COVID-19.

## Materials and methods

This meta-analysis was conducted according to PRISMA guidelines. The protocol was registered (number: CRD42021241307) online (<https://www.crd.york.ac.uk/PROSPERO>).

### Electronic literature search

Two independent investigators (GS and WQ) independently searched PubMed, MEDLINE, Embase, Scopus, and Cochrane library from database inception to 09 April 2021, to identify the relevant studies. No limits were applied for language. The search keywords included “COVID-19” and “lung ultrasound score”. The details of the search strategy are shown in the **Supplementary file S1**. At the same time, the article references were read to find any potential literature that may have met the criteria.

### Study selection and exclusion

Two researchers (GS and WQ) independently screened the titles and abstracts for eligibility. Full papers were assessed to confirm disagreement in existence according to the exclusion criteria by the two researchers. Disagreements were discussed and resolved by involving a third reviewer (XW) for adjudication.

Original studies were eligible if they met the following criteria: (i) observational studies with death as the research endpoint, or studies comparing LUS score in different severities of COVID-19 patients; (ii) quantitative assessment of LUS score using 12-zone/0–36 score protocol, which is the most widely used; (iii) COVID-19 cases could be classified as mild, moderate, severe, or critical, according to the *Guidelines for the Diagnosis and Treatment of Novel Coronavirus (2019-nCoV) Infection by the National Health Commission (Lin and Li, 2020)*.

Studies were ineligible if they: (i) were reviews, abstracts, letters, or case reports/series; (ii) did not report the data necessary for calculating the mean and standard deviation of the LUS score; (iii) did not mention the death/survival outcome or severity of COVID-19; or (iv) were animal studies. If there were several publications from the same study, the study with the most cases and relevant information was included.

The extracted data included the first author of the study, year of publication, country, group and participant number, gender, age, LUS time, and study design. The LUS scores were extracted and stored in the excel sheet. Numeric data were gathered directly from tables, or were inferred by digitizing the figure with GetData Graph Digitizer 2.26 when presented in graphs only (Li et al., 2017). Data extraction was performed independently by two of the reviewers (GS and XW). Disagreements were discussed and resolved by involving a third reviewer (XY) for adjudication.

The quality assessment was performed by the Newcastle-Ottawa Scale (NOS) assessment tool. Two researchers (GS and

WQ) assessed the involved articles separately. Disagreements were solved by a third researcher (XW).

### Statistical analysis

The pooled effects were presented as the weighted mean difference (WMD) with 95% confidence intervals (CIs). Heterogeneity was assessed using the  $I^2$  statistic. If there was no heterogeneity ( $P > 0.1$  or  $I^2 < 50\%$ ), a fixed-effects model was used to estimate the pooled WMD; otherwise, a random-effects model was utilized. Subgroup analyses were conducted based on “Country”, “Male percentage”, “Mean age”, “Patient source”, “LUS time”, and “Study design” when heterogeneity existed. Sensitivity analyses were directed to assess the influence of the individual study on the overall estimate. The symmetry of a funnel plot was analyzed to evaluate possible small sample effects and Begg’s and Egger’s tests were used to evaluate publication bias in the included studies. A  $P$ -value  $< 0.1$  was considered statistically significant for asymmetry. Statistical analyses were performed using Stata (version 14.0; Stata Corp, College Station, TX, USA). Trial sequential analysis (TSA, version 0.9.5.10 Beta) was conducted according to a previous paper (Song et al., 2020).

## Results

### Description of the included studies

A total of 117 potentially relevant publications were identified and reviewed from five databases: 114 from PubMed, 38 from MEDLINE, 89 from Embase, 28 from Scopus, and five from Cochrane library (Figure 1). After application of the inclusion and exclusion criteria, 16 studies were identified (Bosso et al., 2020; de Alencar et al., 2021; Deng et al., 2021; Giorno et al., 2020; Kong et al., 2021; Li et al., 2020; Lichter et al., 2020; Mafort et al., 2021; Paolo et al., 2021; Recinella et al., 2021; Secco et al., 2021; Wangüemert Pérez et al., 2020; Xian et al., 2020; Yasukawa et al., 2021; Ye et al., 2021; Zhu et al., 2021). The baseline characteristics of the included studies are shown in Table 1. All studies were published in these two years. Studies were conducted in Italy, China, Spain, Brazil, USA, and Israel. A total of 1541 patients with COVID-19 were included. In the studies with death as the endpoint, most (77.8%, 7/9) conducted LUS within 24 hours after admission. Seven prospective studies and nine retrospective studies were identified. The Newcastle-Ottawa Scale (NOS) scores ranging 7–9 indicated that there was no low-quality study involved.

### Association of LUS score with mortality risk of COVID-19 and subgroup analysis

The LUS score was significantly higher in the death group compared with the survival group (WMD = 8.21, 95% CI: 4.74–11.67,  $P < 0.001$ , Figure 2). Subgroup analysis was conducted to investigate the possible sources of heterogeneity of death/survival ( $I^2 = 91.8\%$ ,  $P < 0.001$ ) (Table 2). After being stratified by patient source, heterogeneity was slightly decreased. Subgroup analysis indicated that significant results were observed in most of the subgroup analyses.

### Association of LUS score with the severity of COVID-19

Those with mild/moderate, severe and critical COVID-19 had a progressively higher LUS score (critical vs. severe: WMD = 8.78, 95% CI: 4.17–13.38,  $P < 0.001$ ; critical vs. mild/moderate/severe: WMD = 10.00, 95% CI: 6.83–13.17,  $P < 0.001$ ; severe vs. moderate: WMD = 5.96, 95% CI: 3.48–8.44,  $P < 0.001$ ; and severe vs. mild/moderate: WMD = 7.31, 95% CI: 4.45–10.17,  $P < 0.001$ ; Figure 3). However, the LUS score was similar in the moderate

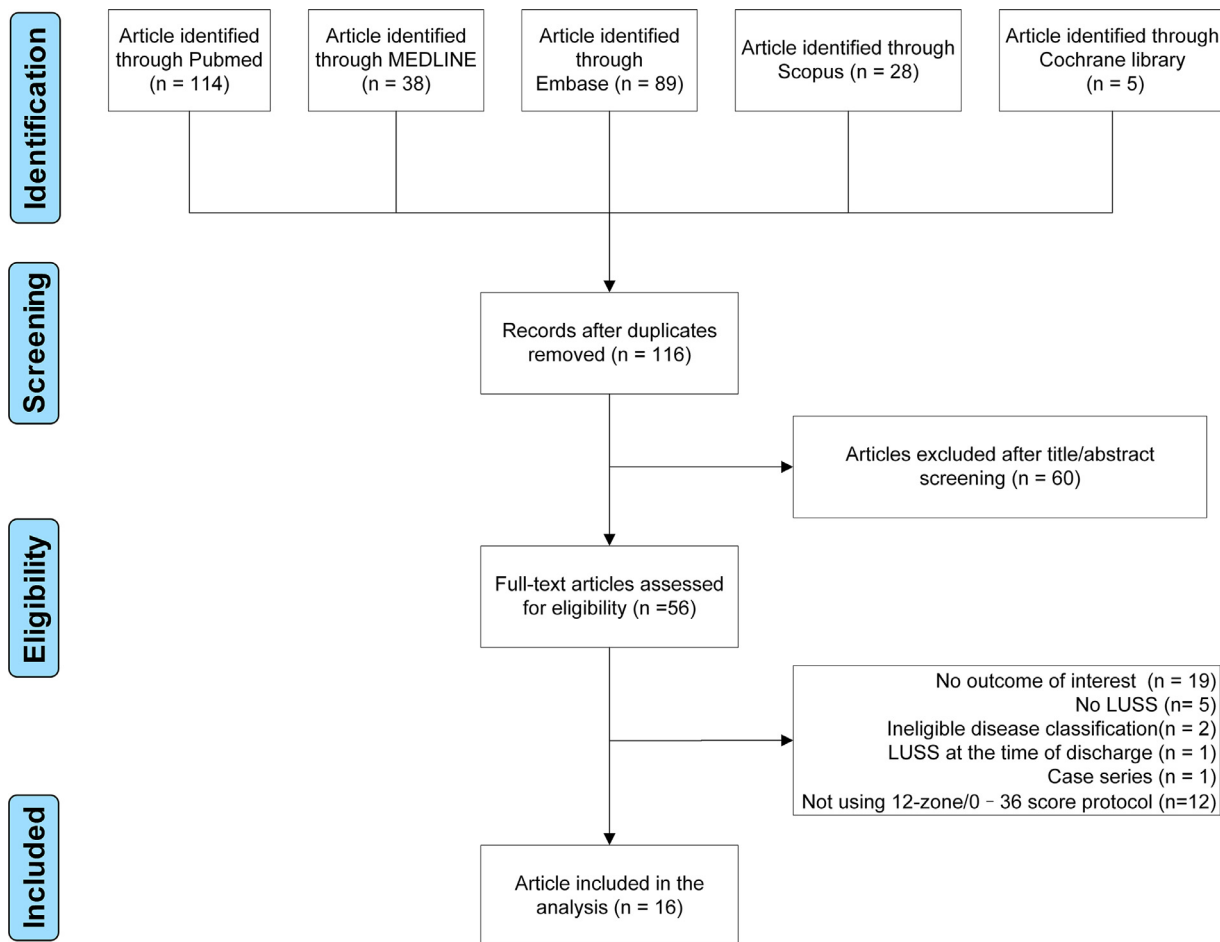


Figure 1. Flow-chart of study selection. LUSS, lung ultrasound score

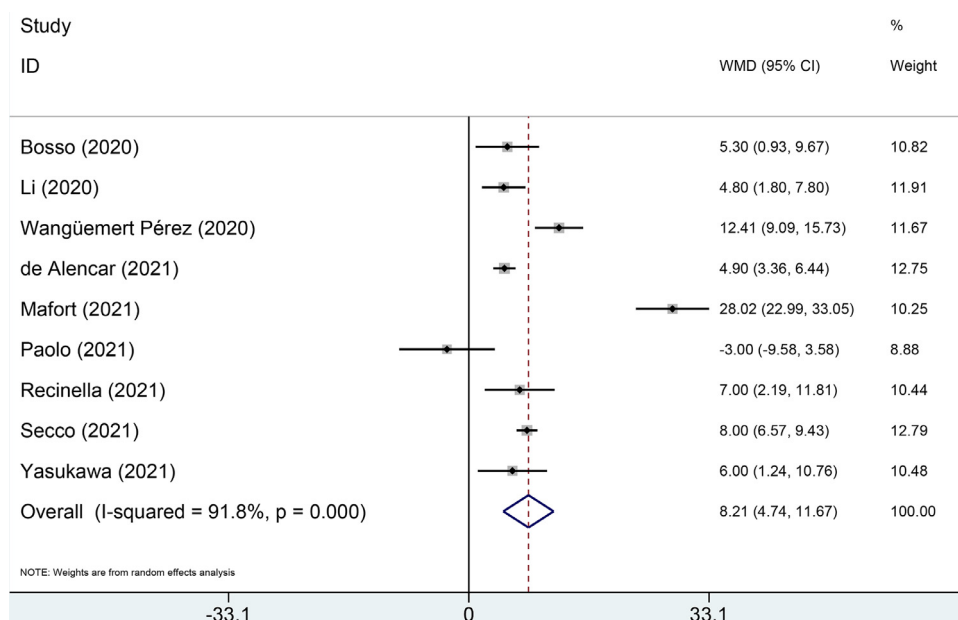


Figure 2. Forest plots for lung ultrasound score between the death and survival groups of COVID-19 patients.

**Table 1**  
The baseline characteristics of the included studies.

No	Study	Year	Country	Group	N	Sex (male%)	Age (years)	LUS time	Study design	NOS score
1	Bosso	2020	Italy	Death	12	75.0	71.7±12.3	Other*	Retrospective study	9
				Survivor	14	64.3	61.1±16.5			
2	Li	2020	China	Death	12	66.7	63.6±19.1	Within 24 hours after admission	Prospective study	9
				Survivor	36	69.4	66.1±12.9			
3	Wangüemert Pérez de Alencar	2020	Spain	Death	10	44.4	82.4±9.9	Within 24 hours after admission	Retrospective study	8
				Survivor	35					
4	de Alencar	2021	Brazil	Death	61	58.3	60.0±15.6	Within 24 hours after admission	Prospective study	9
				Survivor	109					
5	Mafort	2021	Brazil	Death	3	31.8	40.0±11.9	Other*	Retrospective study	8
				Survivor	444					
6	Paolo	2021	Italy	Death	10	75.0	69.0±11.9	Within 24 hours after admission	Prospective study	9
				Survivor	18					
7	Recinella	2021	Italy	Death	11	36.4	90.0±9.6	Within 24 hours after admission	Prospective study	8
				Survivor	26	57.7	80.5±13.7			
8	Secco	2021	Italy	Death	79	67.1	77.0±16.5	Within 24 hours after admission	Prospective study	9
				Survivor	165	67.9	60.0±16.8			
9	Yasukawa	2021	USA	Death	9	61.9	57.9±14.2	Within 24 hours after admission	Prospective study	9
				Survivor	96					
10	Giorno	2020	Brazil	Mild	18	77.8	1.9±4.0	Other*	Retrospective study	9
				Moderate	8	50.0	0.3±2.7			
				Severe	3	37.5	2.4±2.7			
				Critical	5					
11	Lichter	2020	Israel	Mild/moderate	75	57.3	64.2±21.0	Within 24 hours after admission	Prospective study	9
				Severe	31	67.7	72.3±13.0			
				Critical	14	71.4	72.5±24.0			
12	Xian	2020	China	Moderate	15	54.8	60.0±14.3	Other*	Retrospective study	8
				Severe	11					
				Critical	5					
13	Zhu	2020	China	Critical	16	50.0	64.8±11.6	Other*	Retrospective study	9
				Non-critical	32	56.3	62.0±14.3			
14	Deng	2021	China	Mild	6	100.0	29.0±3.0	Other*	Retrospective study	8
				Moderate	29	100.0	30.0±3.7			
				Severe	4	100.0	30.0±2.2			
15	Kong	2021	China	Severe	63	39.7	63.4±12.2	Within 24 hours after admission	Retrospective study	9
				Critical	33	60.6	69.2±12.7			
16	Ye	2021	China	Severe	11	72.7	67.2±15.9	Other*	Retrospective study	7
				Mild/moderate	12	33.3	53.5±13.5			

LUS, lung ultrasound; NOS, Newcastle-Ottawa Scale

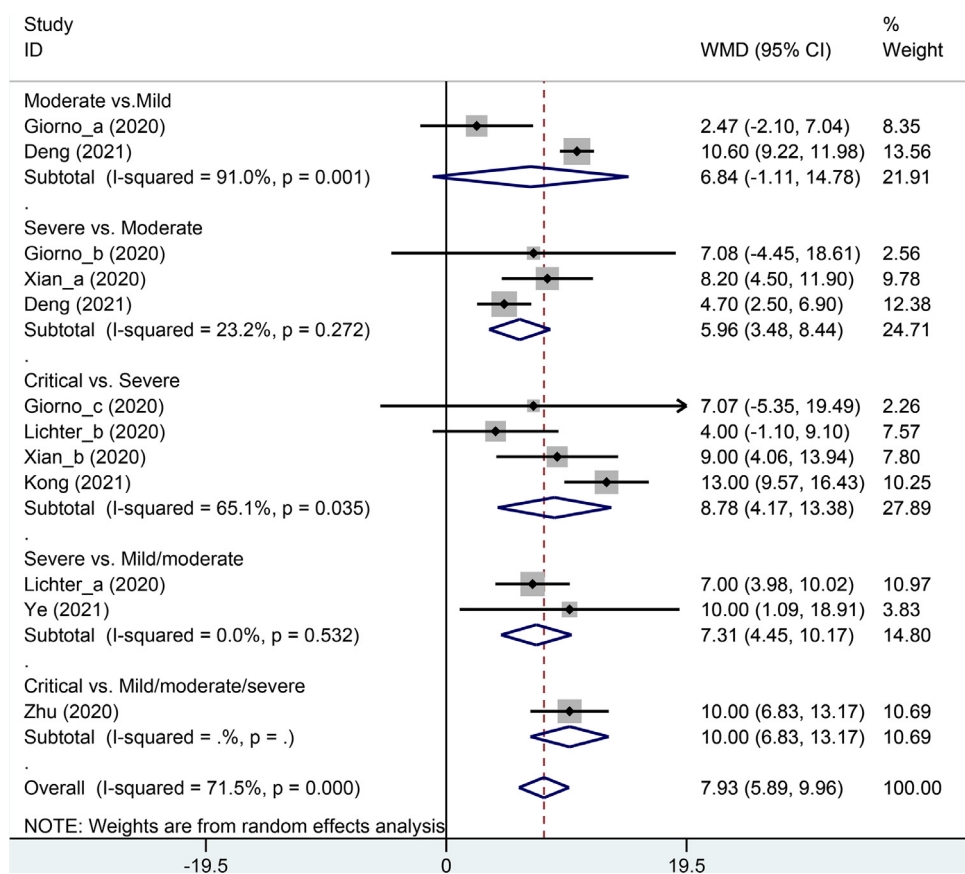
\* lung ultrasound exams were performed as early as possible after admission and being diagnosed with COVID-19.

**Table 2**  
Subgroup analyses of lung ultrasound score between the death and survival groups.

	Number of studies	Test of difference		Test of Heterogeneity	
		WMD (95% CI)	P value	I <sup>2</sup> (%)	P value
Country					
Europe	5	6.73 (3.21–10.25)	<0.001	79.1	0.001
China	1	4.80 (1.81–7.80)	0.002	-	-
Brazil	2	16.33 (-6.33–33.99)	0.158	98.7	<0.001
USA	1	6.00 (1.24–10.76)	0.014	-	-
Male percentage					
> 50%	7	5.46 (3.53–7.39)	<0.001	65.5	0.008
< 50%	2	20.10 (4.80–35.39)	0.010	96.1	<0.001
Mean age					
> 65 years	6	6.44 (3.50–9.39)	<0.001	78.1	<0.001
< 65 years	3	12.84 (-0.20–25.88)	0.054	97.3	<0.001
Patient source					
Emergency department	3	6.25 (3.79–8.70)	<0.001	76.9	0.013
Intensive care unit	2	1.47 (-6.09–9.04)	0.702	77.6	0.035
General ward	3	8.77 (4.48–13.06)	<0.001	67.0	0.048
Outpatient	1	28.02 (22.99–33.05)	<0.001	-	-
LUS time					
Within 24 hours after admission	7	6.33 (3.93–8.72)	<0.001	79.9	<0.001
Other	2	16.62 (-5.64–38.89)	0.143	97.8	<0.001
Study design					
Prospective study	6	5.43 (3.27–7.59)	<0.001	71.0	0.004
Retrospective study	3	15.16 (3.57–26.75)	0.010	95.6	<0.001

CI, confidence interval; WMD, weighted mean difference





**Figure 3.** Subgroup analysis of weighted mean difference (WMD) in lung ultrasound score between different severities of COVID-19.

group compared with the mild group (WMD = 6.84, 95% CI: -1.11–14.78,  $P = 0.092$ , Figure 3).

#### Sensitivity analysis, publication bias and TSA

To evaluate the robustness of the results, sensitivity analyses were performed by sequentially removing each study. No apparent change occurred when an individual study was omitted. No publication bias was observed in evaluation of the funnel plots for the death and survival groups, and this finding was confirmed by Begg's ( $P = 0.602$ ) and Egger's ( $P = 0.588$ ) tests. No publication bias was revealed in evaluation of the funnel plots for LUS score with severity of COVID-19, and this finding was confirmed by Begg's ( $P = 0.837$ ) and Egger's ( $P = 0.348$ ) tests. The cumulative Z-curve passed both the traditional boundary and trial sequential monitoring boundary, suggesting sufficient evidence of such a difference between the death and survival groups (Figure 4).

#### Discussion

This is the first meta-analysis to comprehensively summarize the association of LUS score with mortality and severity of COVID-19. This meta-analysis found that the LUS score was a potential prognostic index for mortality. Additionally, the LUS score was a risk stratification and monitoring tool for COVID-19, which was confirmed by sensitivity analysis, publication bias test and TSA.

Since the COVID-19 outbreak, the number of confirmed cases has increased exponentially. Although quarantine and face-mask use have been reported as effective preventive measures (Hantoko et al., 2021), some countries are facing second and third waves of the COVID-19 pandemic. Hospitals are currently overcrowded. A serious problem that is arising is how to quickly and

easily evaluate the severity of COVID-19, which could efficiently allocate medical resources. Meanwhile, rapid and accurate prediction of clinical adverse outcomes is central to the management of global outbreaks of infection. Stratification by this predicted tool, most commonly for death, can help doctors make treatment-related decisions.

Numerous studies have explored several prognostic factors for adverse outcomes of COVID-19, including: male sex, old age, severe obesity, hypertension, diabetes mellitus, and cigarette smoking (Hatmi, 2021). Other studies have used hematological and biochemical indices, such as C-reactive protein, IL-6 and D-dimer (Kotru et al., 2021), as alternative predictive tools. Radiologists have measured computed tomography (CT) scores to predict composite adverse outcomes (Xu et al., 2020). However, CT may not be suitable for critically ill patients because of the risks of patient transport and infecting others. The ionizing radiation of CT is a concern for children and pregnant women. The current COVID-19 pandemic has caused serious economic burden, and CT examination has been overburdened. Safe usage of CT scanners to image COVID-19 patients is also logistically challenging and can overwhelm the available resources (Chan et al., 2020).

Ultrasound has several advantages such as its ease of sterilization, low cost and absence of radiation. In recent years, LUS has emerged as an accurate diagnostic tool for respiratory diseases. LUS is also an excellent monitoring tool. During the pandemic, LUS has been applied to diagnose, monitor and follow-up cases with COVID-19. New ultrasound technologies, such as portable pocket-sized ultrasound or 5G-based robot-assisted remote ultrasound, may play an important role in emergency units and ICUs in the future of anti-COVID-19 (Ye et al., 2021).

A sonographer performs the specific LUS protocol then calculates the LUS score, which is defined as the sum of the scores

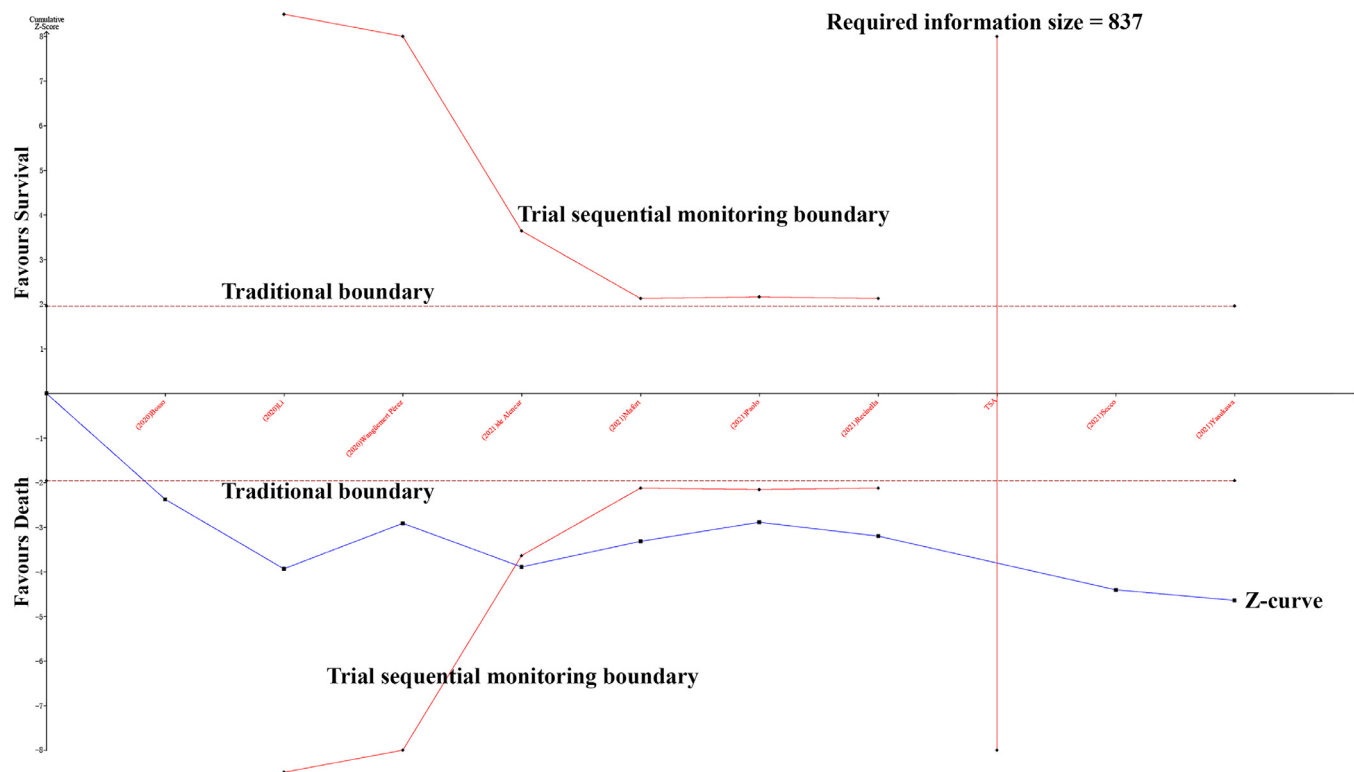


Figure 4. Comparison of the lung ultrasound score between death and survival groups by trial sequential analysis.

of each exam zone by measuring lung aeration loss (Yin et al., 2019). Although there is no consensus about the most efficient and accurate LUS protocol, 12-zone/0–36 score is the most widely used protocol in COVID-19 patients. Previous studies have found that there were similarities between different protocols: Wangüemert Pérez et al. found that the results of 8-zone/0–24 score protocol were similar to the 12-zone/0–36 score protocol in their study (Wangüemert Pérez et al., 2020); Ramos et al. revealed that the results of the 8-zone/0–24 score protocol were similar to the 14-zone/0–42 score protocol in their cohort of COVID-19 patients (Ramos Hernández et al., 2021).

The current results revealed that survivors had a lower LUS score than the deaths. The explanation is that LUS could allow a semi-quantitative estimation of the extravascular lung water and, indirectly, of the blood oxygenation (Zong et al., 2020). A lower LUS score means less impaired aeration of the lung in COVID-19 patients (Bosso et al., 2020). The reason that the LUS score is associated with mortality of COVID-19 is that the LUS score has been found to be associated with several proven COVID-19 risk factors, including: CT severity score, C-reactive protein, IL-6, D-dimer, and PaO<sub>2</sub>/FiO<sub>2</sub>. The LUS score has been significantly positively correlated with the CT severity score (Deng et al., 2020; Nouvenne et al., 2020; Zhu et al., 2021), C-reactive protein (Møller-Sørensen et al., 2020), IL-6 (Rojatti et al., 2020), and D-dimer (Perrone et al., 2020). However, the LUS score has been significantly negatively correlated with PaO<sub>2</sub>/FiO<sub>2</sub> (Bosso et al., 2020; Li et al., 2020; Perrone et al., 2020; Rojatti et al., 2020; Secco et al., 2021). PaO<sub>2</sub>/FiO<sub>2</sub> has been found to be lower in COVID-19 patients, particularly those with the worst outcomes (Grasselli et al., 2020). PaO<sub>2</sub>/FiO<sub>2</sub> can be considered as a global index of tissue aeration. All these correlations illustrate that a high LUS score is a potential risk factor for COVID-19 patients.

In the studies in this meta-analysis, some found that the LUS score was associated with other adverse outcomes, including the need for respiratory support, hospitalization, or ICU admission (de Alencar et al., 2021; Yasukawa et al., 2021); more evidence is

needed to confirm these findings. Meanwhile, the LUS score was also associated with the severity of COVID-19. According to the results of this meta-analysis, a higher LUS score means a more severe COVID-19 condition. Recently, three studies already used the LUS score as a risk stratification tool for COVID-19 patients (Ji et al., 2020; Lichter et al., 2020; Rubio-Gracia et al., 2021). Several of the involved papers proposed their cut-off value of the LUS score for mortality and severity of COVID-19 (de Alencar et al., 2021; Li et al., 2020; Lichter et al., 2020; Recinella et al., 2021; Secco et al., 2021; Zhu et al., 2021). The cut-off values for predicting survival were 13 (Secco et al., 2021), 16 (de Alencar et al., 2021), 17 (Recinella et al., 2021), 18 (Lichter et al., 2020), and 22.5 (Li et al., 2020), respectively. The cut-off value for predicting critical COVID-19 was 7, with a sensitivity of 80.8% and specificity of 95.8% (Zhu et al., 2021). The application of the LUS score as a risk stratification tool needs to be discussed and verified by experts in the future.

**Limitations**

There were several limitations to this study: first, most studies were single-center. Single race and the small sample size cannot be ignored. These disadvantages could reduce the credibility of the conclusion of this study. Second, all LUS exams in the involved studies were performed as early as possible (most within 24 hours after admission); however, some studies did not mention the specific details of the LUS exam time. Third, some underlying confounders may not be adjustable in the involved studies, such as the therapy for COVID-19 and comorbidities in each group.

**Conclusion**

The LUS score was associated with mortality and severity of COVID-19. The LUS score has the potential to be a risk stratification tool for COVID-19 patients.

**Conflict of interest**

None declare.

**Ethical approval**

Not applicable.

**Funding**

None declare.

**Supplementary materials**

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.ijid.2021.06.026](https://doi.org/10.1016/j.ijid.2021.06.026).

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