Thieme

Risk Stratification in COVID-19 Pneumonia – Determining the Role of Lung Ultrasound

Risikostratifizierung bei COVID-19-Pneumonie – Bestimmung der Rolle des Lungen-Ultraschalls

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ABSTRACT

LUS patterns of COVID-19 pneumonia have been described and shown to be characteristic. The aim of the study was to predict the prognosis of patients with COVID-19 pneumonia, using a score based on LUS findings.

Materials and Methods An observational, retrospective study was conducted on patients admitted to Niguarda hospital with a diagnosis of COVID-19 pneumonia during the period of a month, from March 2nd to April 3rd 2020. Demographics, clinical, laboratory, and radiological findings were collected. LUS was performed in all patients. The chest was divided into 12 areas. The LUS report was drafted using a score from 0 to 3 with 0 corresponding to A pattern, 1 corresponding to well separated vertical artifacts (B lines), 2 corresponding to white lung and small consolidations, 3 corresponding to wide consolidations. The total score results from the sum of the scores for each area. The primary outcome was endotracheal intubation, no active further management, or death. The secondary outcome was discharge from the emergency room (ER).

Results 255 patients were enrolled. 93.7 % had a positive LUS. ETI was performed in 43 patients, and 24 received a DNI order. The general mortality rate was 15.7 %. Male sex (OR 3.04, p = 0.014), cardiovascular disease and hypertension (OR 2.75, p = 0.006), P/F (OR 0.99, p < 0.001) and an LUS score > 20 (OR 2.52, p = 0.046) were independent risk factors associated with the primary outcome. Receiver operating characteristic (ROC) curve analysis for an LUS score > 20 was performed with an AUC of 0.837. Independent risk factors associated with the secondary outcome were age (OR 0.96, p = 0.073), BMI (OR 0.87, p = 0,13), P/F (OR 1.03, p < 0.001), and LUS score < 10 (OR 20.9, p = 0.006). ROC curve analysis was performed using an LUS score < 10 with an AUC 0.967.

Conclusion The extent of lung abnormalities evaluated by LUS score is a predictor of a worse outcome, ETI, or death. Moreover, the LUS score could be an additional tool for the safe discharge of patient from the ER.

ZUSAMMENFASSUNG

LUS-Muster einer COVID-19-Pneumonie wurden beschrieben und erwiesen sich als charakteristisch. Ziel der Studie war es, die Prognose von Patienten mit COVID-19-Pneumonie durch einen auf LUS-Befunden basierenden Score vorherzusagen.

Material und Methoden Eine retrospektive Beobachtungsstudie wurde an Patienten durchgeführt, die im Zeitraum eines Monats vom 2. März bis 3. April 2020 mit der Diagnose einer COVID-19-Pneumonie in das Niguarda-Krankenhaus eingeliefert wurden. Demografische Daten, klinische, labortechnische und radiologische Befunde wurden erhoben. LUS

wurde bei allen Patienten durchgeführt. Der Thorax wurde in 12 Areale unterteilt. Der LUS-Bericht wurde anhand eines Scores von 0 bis 3 erstellt, wobei 0 einem A-Muster entspricht, 1 gut abgegrenzten vertikalen Artefakten (B-Linien), 2 einer weißen Lunge und kleinen Konsolidierungen, 3 größeren Konsolidierungen. Der Gesamtscore ergibt sich aus der Summe der Scores für jedes Areal. Der primäre Endpunkt war die endotracheale Intubation (ETI), keine weiteren aktiven Maßnahmen oder der Tod. Der sekundäre Endpunkt war die Entlassung aus der Notaufnahme.

Ergebnisse 255 Patienten wurden in die Studie aufgenommen; 93,7 % davon hatten einen positiven LUS. Bei 43 Patienten wurde eine ETI durchgeführt, bei 24 gab es eine DNI (Do-not-intubate)-Anordnung. Die allgemeine Sterblichkeitsrate betrug 15,7 %. Männliches Geschlecht (OR 3,04; p = 0,014), kardiovaskuläre Erkrankungen und Hypertonie (OR 2,75; p = 0,006), P/F (OR 0,99; p < 0,001) und ein LUS-Score > 20 (OR 2,52; p = 0,046) waren unabhängige Risikofaktoren, die mit dem primären Outcome assoziiert waren. Die ROC-Kurvenanalyse (Receiver Operating Characteristic) für einen LUS-Score > 20 ergab einen AUC von 0,837. Unabhängige, mit dem sekundären Outcome assoziierte Risikofaktoren waren Alter (OR 0,96; p = 0,073), BMI (OR 0,87; p = 0,13), P/F (OR 1,03; p < 0,001) und LUS-Score < 10 (OR 20,9; p = 0,006). Die ROC-Kurvenanalyse unter Verwendung eines LUS-Scores < 10 ergab einen AUC von 0,967.

Schlussfolgerung Das Ausmaß der Lungenanomalien, die mittels LUS-Score bewertet wurden, ist ein Prädiktor für ein schlechteres Outcome, ETI oder Tod. Darüber hinaus könnte der LUS-Score eine Zusatzmethode für die sichere Entlassung von Patienten aus der Notaufnahme sein.

On Feb 21, 2020, the first person-to-person transmission of SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus-2) in Italy was reported. The clinical manifestations of SARS-CoV-2 infection are broad, ranging from a flu-like syndrome to a severe form of interstitial pneumonia with respiratory failure [1].

During epidemic outbreaks, characterized by massive admittance to hospital emergency rooms (ERs), it is important to set clear management paths in order to quickly allocate resources and to quickly stratify patients at higher risk and needing closer monitoring. It is also crucial to safely discharge patients, thereby avoiding the collapse of the hospital system. Nevertheless, many facilities were unprepared for the impact of COVID-19, due to a lack of knowledge and the absence of tools for risk stratification.

Since the beginning of the pandemic emergency, clinical and laboratory predictors of disease severity have been identified. Older age, male sex, hypertension, cardiovascular disease, diabetes, and higher body mass index (BMI) were found to be associated with a severe form of COVID-19 pneumonia, death, or admission to the intensive care unit (ICU) [2, 3]. Different biochemical tests, such as C-Reactive Protein (CRP), ferritin, D-dimer, lymphocytopenia, thrombocytopenia and levels of Interleukin 6 (IL6), were also associated with a worse outcome [4]. Liang et al. validated a prognostic score (including ten items such as X-ray abnormality and demographic, anamnestic, and laboratory data) to predict a composite risk of death, ICU admission, and need for mechanical ventilation [5].

Colombi et al. proposed the extent of computerized tomography (CT) lung abnormality detected by visual or software quantification as a predictor of ICU admission and death [6].

Even if useful for patient risk stratification and management, widespread use of chest CT scan can be difficult due to reduced availability, the risk of SARS-COV-2 spreading, and the difficulties related to the transport of critically ill patients.

On the other hand, lung ultrasound (LUS) has many advantages so that it has been increasingly used over the past few decades, especially in the critical care and emergency setting. LUS is quick to perform (5 minutes for most uses), it needs relatively low-cost equipment, and it can be repeated at the bedside with no side effects [7].

LUS is an important tool in managing patients with lung disease, with an established role in clinical practice. The sensitivity of LUS for the evaluation of pneumonia and acute respiratory distress syndrome (ARDS) is similar to chest CT scan and superior to standard chest radiography [8–10].

Some authors have emphasized the utility of LUS during the COVID-19 pandemic outbreak. Ultrasound can be useful for the early evaluation of COVID-19 pneumonia severity and can be used to monitor the evolution of the disease and the response to lung recruitment maneuvers and prone position [11–14]. However, all the previous studies have a small sample size. The aim of this study is to verify, in a large cohort, the usefulness of LUS for the early identification of patients with COVID-19 pneumonia and to stratify those at higher risk of worsening.

Methods

This retrospective, observational study was carried out in Grande Ospedale Metropolitano Niguarda in Milan, Lombardy, Italy. Niguarda Hospital handled the highest number of Covid-19 hospitalizations in Milan. The study was approved by the institutional ethics committee of Niguarda Hospital (protocol number ID 3907). Informed consent was waived due to the retrospective and observational nature of the study according to the Italian law on observational studies.

Study participants

From March 2nd 2020 to April 3rd 2020, 1178 patients with confirmed COVID-19 were admitted to the ER. 255 not consecutive patients were assessed by LUS at presentation and thus enrolled in the study. Based on the WHO interim guidance, a confirmed case of COVID-19 was defined by a positive result of real-time reverse transcriptase–polymerase chain reaction (RTPCR) assay of nasal and pharyngeal swabs [15].

Data collection

Demographics, comorbidities, clinical data, laboratory tests with blood gas analysis (BGA) obtained at admission were recorded. We recorded radiologic assessments with X-ray and chest CT when performed. Ultrasound was performed in all patients at hospital presentation. Furthermore, we collected data on oxygen administration and ventilation support applied: CPAP (Continuous Positive Airway Pressure), NIV (Noninvasive Ventilation), ETI (Endotracheal Intubation).

Ultrasound

Ultrasound was performed using a portable ultrasound machine MyLab Alpha (Easote, Italy). It was prepared using a single plastic cover for the transducer and the tablet was cleaned with alcohol after every use. The machine was dedicated solely to patients suspected of having COVID-19 infection. The examination was carried out using a convex transducer (1–8 MHz).

The operative protocol is described below, according to international evidence-based recommendations for point-of-care lung ultrasound [8]:

- Examination was performed using focal point modality (no multifocusing) and setting the focal point on the pleura line.
- The thorax was initially assessed by placing the transducer orthogonal to the ribs to find the best location. The transducer was then turned as if to use intercostal scans, in order to cover the widest surface.
- The chest was divided into 12 areas: 2 anterior, 1 lateral and 3 posterior, on both sides (▶ **Supplementary Fig. 1**).

The LUS report was drafted using a score from 0 to 3 according to recent publications [16, 17]:

- 0 corresponding to A patten (due to horizontal reverberations of the pleural line – A lines – and mirror effects typical of the normal lung surface)
- 1 corresponding to well separated vertical artifacts (B lines). Pleural line can be either regular or irregular.
- 2 corresponding to white lung (coalescence of many vertical artifacts in more extended echogenic patterns, in which the individual artifacts are still recognizable or fused in a single homogeneous subpleural echogenic area) and small consolidations.
- 3 corresponding to wide consolidations.

Patients were assessed also by point-of-care echocardiography: Left Ventricular Ejection Fraction (LVEF), Tricuspid Annulus Plane Systolic Excursion (TAPSE), and Inferior Vena Cava (IVC) Collapsibility Index were recorded. The LVEF was recorded visually (only verbal stratification in the added protocol). Right heart assessment is assessed according to the protocol.

Outcome

The primary outcome was a composite of death, need for mechanical ventilation, and dispatch of no active further management (i. e., not for intubation or active resuscitation). For death, in-hospital mortality was considered for patients admitted to the ward, while 30-day mortality was considered for patients discharged directly from the ER.

Evaluation for ETI eligibility was performed in patients with severe respiratory insufficiency not responding to NIV. A dispatch of no active further management was issued by an expert anesthesiologist in agreement with the emergency physician, considering the severity of the disease, patient age, and comorbidities. In the case of disagreement, a second opinion by a senior anesthesiologist was obtained. We decided to consider this combined outcome because all three are indicators of disease severity. Hereafter these patients will be defined as the outcome group. The secondary outcome was discharge from the ER.

Statistical Analysis

Continuous data are expressed as means with standard deviations or as medians with interquartile ranges, depending on normality. Categorical variables are provided with percentages. The Mann-Whitney U test, χ^2 test, and Fisher exact test were conducted when appropriate. Univariable and backward stepwise multivariable logistic regression analysis was used to test the association between potential predictors and the outcome. In the first multivariate analysis, assessing the primary endpoint, the variable LUS score was categorized in two levels with a cut-off set at 20 (< 20 vs. ≥ 20). The second multivariate analysis was performed to investigate if the LUS score could be useful for safe discharge from the ED. The outcome in these models was defined as discharge from the ED and the LUS score threshold was lowered to 10. Receiver operating characteristic (ROC) curve analysis was performed for each model and the area under the ROC (AUC) was used to assess the performance of the discrimination models based on independent predictors. All analyses were performed with the use of R (A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

Results

A total of 1178 patients with SARS-CoV-2 infection were evaluated in our ER during the study period. 255 non-consecutive patients (21.6 % of the total) were assessed by LUS at presentation and were thus enrolled in the study. 172 out of 255 patients (67.5 %) were men, and the mean age was 58.4 years (± 15.6).

Among them, 65 % had at least one coexisting illness with hypertension (109/255; 42.7 %), diabetes (40/255; 15.7 %) and cardiovascular disease (110/255; 43.1 %) being the most frequent. 49 patients out of 243 (20.2 %) had a BMI > 30.

Patients presented to the ER with a median delay of 7 days (IQR 5–10) from symptom onset. The predominant symptom on admission was fever (233/255; 91.4 %), followed by cough (149/255; 58.4 %) and dyspnea (107/255; 42 %). Demographic, comorbidity, clinical and laboratory findings are reported (▶ **Table 1, 2**, ▶ **Supplementary Table 1**).

239 out of 255 (93.7 %) patients had a positive LUS. 250 patients underwent chest CT scan, positive in 248 (99 %). Chest X-ray was performed only in 42 patients and only 27 (64 %) had positive results. There was concordance between LUS and chest

▶ Table 1 Demographics and clinical findings.

		exitus/ETI/DNI			discharge from the ER		
		no	yes	p-value	no	yes	p-value
demographics characteristics							
male, N (%)	172 (67.5)	112 (61.2)	60 (83.3)	0.001	156 (70.3)	16 (48.5)	0.013
female, N (%)	83 (32.5)	71 (38.8)	12 (16.7)	0.001	66 (29.7)	17 (51.5)	0.013
age, mean (sd)	58.4 (± 15.6)	55.7 (± 15.1)	65.3 (± 14.8)	< 0.001	60 (± 14.9)	47.5 (± 16.4)	< 0.001
comorbidities, N (%)							
patients with no comorbidities	90 (35.3)	76 (41.1)	14 (20)	0.002	72 (32.4)	18 (54.5)	0.013
BMI, median [IQR]	26 [24–29]	26 [23–28]	27 [25–30.75]	0.031	26 [24–29]	23.5 [22–25]	< 0.001
hypertension	109 (42.7)	63 (34.4)	46 (63.9)	< 0.001	101 (45.5)	8 (24.2)	0.021
diabetes	40 (15.7)	22 (12)	18 (25)	0.010	38 (17.1)	2 (6.1)	0.077
immune suppression	13 (5.1)	7 (3.8)	6 (8.3)	0.141	13 (5.9)	0 (0)	0.157
neoplasia	10 (3.9)	5 (2.7)	5 (6.9)	0.119	10 (4.5)	0 (0)	0.243
PULMONARY disease	25 (9.8)	12 (6.6)	13 (18.1)	0.005	24 (10.8)	1 (3)	0.134
cardiovascular disease	110 (43.1)	64 (35)	46 (63.9)	< 0.001	102 (45.9)	8 (24.2)	0.019
vascular disease	17 (6.7)	6 (3.3)	11 (15.3)	0.001	17 (7.7)	0 (0)	0.087
chronic renal failure	13 (5.1)	6 (3.3)	7 (9.7)	0.035	13 (5.9)	0 (0)	0.157
symptoms, N (%)							
days from symptom onset, median [IQR]	7 [5–10]	7 [5–10]	6.5 [4–10]	0.404	7 [5–10]	6 [3–7]	0.043
fever	233 (91.4)	167 (91.3)	66 (91.7)	0.916	205 (92.3)	28 (84.8)	0.153
cough	149 (58.4)	111 (60.7)	38 (52.8)	0.251	129 (58.1)	20 (60.6)	0.786
dyspnea	107 (42)	65 (35.5)	42 (58.3)	0.001	101 (45.5)	6 (18.2)	0.003
rhinitis and/or conjunctivitis	7 (2.7)	6 (3.3)	1 (1.4)	0.406	4 (1.8)	3 (9.1)	0.048
asthenia and/or myalgia	36 (14.1)	27 (14.8)	9 (12.5)	0.642	28 (12.6)	8 (24.2)	0.073
dysgeusia and/or anosmia	18 (7.1)	16 (8.7)	2 (2.8)	0.094	14 (6.3)	4 (12.1)	0.190
headache	17 (6.7)	13 (7.1)	4 (5.6)	0.655	11 (5)	6 (18.2)	0.004
gastrointestinal	39 (15.3)	32 (17.5)	7 (9.7)	0.121	28 (12.6)	11 (33.3)	0.002
syncope	8 (3.1)	7 (3.8)	1 (1.4)	0.315	8 (3.6)	0 (0)	0.325
arrhythmia	5 (2.0)	3 (1.6)	2 (2.8)	0.436	5 (2.3)	0 (0)	0.497

ETI: endotracheal intubation; DNI: do not intubate; ER: emergency room; N: number; IQR: interquartile range; sd: standard deviation; BMI: body mass index.

CT scan in 236/250 (94.4%) patients (sensitivity 96.2%; specificity 60%). Most patients had a normal LVEF, TAPSE and an IVC Collapsibility Index > 50% (see ▶ Table 2).

102 out of 255 (40%) patients received only oxygen supplementation, whereas 77/255 (30.1%) were treated with NIV/CPAP. ETI was performed in 43/255 (16.9%) patients, and 24/255 (9.4%) received a dispatch of no active further management. The median length of hospital stay (LOS) was 12 days (IQR 12–17). The general mortality was 15.7% (40/255), and the in-hospital mortality was 18% (40/222) (▶ Supplementary Table 1).

The outcome group consisted of 72/255 (28.2%) patients. They were significantly older (65.3 ± 14.8 vs. 55.7 ± 15.1; p < 0.001), had a higher prevalence of hypertension (63.9% vs. 34.4%; p < 0.001), cardiovascular disease (63.9% vs. 35%; p < 0.001) and diabetes (25% vs. 12%; p = 0.014), and had a lower P/F ratio (ratio of arterial oxygen partial pressure to fractional inspired oxygen) (233, [IQR 111–298] vs. 319, [IQR 275–357]; p < 0.001) and a higher LUS score (17.3 ± 8.8 vs. 10.8 ± 7.3; p < 0.001) (▶ Table 1, 2, ▶ Supplementary Table 1).

After performing backward stepwise multivariable analysis, male sex (OR 3.04, 95% CI 1.30–7.78, p 0.014), hypertension and cardiovascular disease (OR 2.75, 95% CI 1.35–5.72, p 0.006), P/F (OR 0.99, 95% CI 0.99–0.99 p < 0.001), and an LUS score > 20 (OR 2.52, 95% CI 1.01–6.31, p 0.046) were identified as independent risk factors associated with the primary outcome (▶ Table 3). Receiver operating characteristic (ROC) curve analysis

▶ **Table 2** Laboratory and ultrasound findings.

		exitus/ETI/DNI			discharge from the ER		
		no	yes	p-value	no	yes	p-value
laboratory findings, median [IQR]							
CRP, g/dL	6.3 [1.8–10.1]	4.1 [1.2–8.4]	11.2 [6.6–16.75]	< 0.001	7.3 [2.8–11.2]	0.7 [0.2–2]	< 0.001
white blood cells, cell/L^{-1}	6.04 [4.58–8.13]	5.67 [4.39–7.72]	6.9 [5.31–9.95]	0.002	6.3 [4.7–8.7]	5.12 [4.2–6.3]	0.043
lymphocytes, cell/L^{-1}	1.04 [0.77–1.38]	1.1 [0.83–1.4]	0.89 [0.59–1.23]	0.002	1.03 [-]0.76–1.03	1.35 [0.82–1.67]	0.052
platelets, cell/L^{-1}, mean (sd)	203 (± 91)	207 (± 88)	191 (± 97)	0.217	200 (± 93)	221 (± 70.8)	0.204
creatinine, mg/dL	0.93 [0.73–1.14]	0.9 [0.69–1.04]	1.06 [0.85–1.37]	< 0.001	0.94 [0.73–1.14]	0.91 [0.74–1.12]	0.678
total bilirubin, mg/dL	0.49 [0.35–0.68]	0.47 [0.33–0.6]	0.59 [0.40–0.83]	0.007	0.5 [0.36–0.7]	0.44 [0.26–0.56]	0.065
INR	1.12 [1.06–1.2]	1.11 [1.05–1.16]	1.16 [1.11–1.24]	< 0.001	1.13 [1–1.2]	1.1 [1.06–1.12]	0.037
aPTT ratio	1.06 [0.95–1.2]	1.03 [0.96–1.16]	1.15 [1.02–1.26]	< 0.001	1.09 [0.98–1.22]	0.98 [0.88–1.05]	0.001
pH	7.47 [7.44–7.50]	7.47 [7.4–7.50]	7.47 [7.44–7.50]	0.915	7.47 [7.45–7.50]	7.44 [7.43–7.46]	0.016
pCO$_2$, mmHg, mean (sd)	32 (± 5)	32.6 (± 4.9)	30.6 (± 5.3)	0.011	31.8 (± 5)	33.8 (± 6.2)	0.104
pO$_2$, mmHg	69 [60–78]	69 [61–78]	65 [54–76]	0.065		80 [77–90]	< 0.001
F$_i$O$_2$	0.21 [0.21–0.21]	0.21 [0.21–0.21]	0.21 [0.21–0.80]	< 0.001	67 [58–75]	0.21 [0.21–0.21]	0.004
P/F ratio	300 [233–341]	319 [275–357]	233 [111–298]	< 0.001	290 [222–333]	380 [366–428]	< 0.001
S$_p$O$_2$ %	95 [93–97]	95 [93–97]	93.5 [89.8–96]	< 0.001	94 [92–96]	97 [96–98]	< 0.001
ultrasound findings							
LUS score, mean (sd)	12.6 (± 8.3)	10.8 (± 7.3)	17.3 (± 8.8)	< 0.001	14.0 (± 7.8)	3.2 (± 3.7)	< 0.001
Pleural effusion, N (%)	27 (10.6)	20 (10.9)	7 (9.7)	0.964	27 (12.2)	0 (0)	0.075
LVEF							
normal, N (%)	201 (94.8)	147 (96.7)	54 (90)	0.089	179 (94.2)	22 (100)	0.259
reduced, N (%)	11 (5.2)	5 (3.3)	6 (10)		11 (5.8)	0 (0)	
TAPSE, median [IQR]	25 [22–27]	25 [23–28]	24 [21–26]	0.109		23 [21.5–26.5]	0.225
IVC (Collapsibility Index)							
< 30 %	8 (4)	3 (2.1)	5 (9.1)	0.081	7 (3.9)	1 (4.5)	0.097
30–50 %	26 (12.9)	19 (12.9)	7/12.7		20 (11.1)	6 (27.3)	
> 50 %	168 (83.2)	124 (85)	44 (78.2)		153 (85)	15 (68.2)	

ETI: endotracheal intubation; DNI: do not intubate; ER: emergency room; N: number; IQR: interquartile range; sd: standard deviation; CRP: C-reactive protein; INR: international normalized ratio; aPTT: activated partial thromboplastin time; LUS: lung ultrasound; LVEF: left ventricular ejection fraction; TAPSE: tricuspid annular plane systolic excursion; IVC: inferior vena cava.

was performed using a cut-off LUS score > 20 and an AUC 0.837 was obtained (▶ **Fig. 1**).

Patients discharged from the ER were younger (47.5 ± 16.4 vs. 60 ± 14.9; p < 0.001), had a lower BMI (23.5 [22–25] vs. 26 [24–29]; p < 0.001) and presented a lower frequency of cardiovascular disease and hypertension and a higher P/F (380 [366–428] vs. 290 [222–333]; p < 0.001). The LUS score was significantly different using a cut-off of < 10 (28 (33.7 %) vs. 55 (66.3 %) p < 0.001) (▶ **Table 1, 2**).

We performed backward stepwise multivariable analysis. Independent risk factors associated with secondary outcome were age

(OR 0.96, 95 % CI 0.93–1.00, p = 0.073), BMI (OR 0.87, 95 % CI 0.72–1.03, p = 0.13), P/F (OR 1.03 95 % CI 1.02–1.05, p < 0.001), and LUS score < 10 (OR 20.9, 95 % CI 3.51–3.94, p = 0.006) (▶ **Table 4**).

Receiver operating characteristic (ROC) curve analysis was performed using < 10 LUS score as the cut-off with an AUC of 0.967 (▶ **Fig. 2**).

All discharged patients were alive 30 days from discharge (telephone follow-up).

▶ **Table 3** Logistic regression analysis for the relationship between baseline clinical and LUS parameters and death/ETI/DNI.

	univariable analysis		multivariable analysis			
	OR	p-value	adjOR	p-value	adjOR	p-value
age	1.04 (1.02–1.06)	0.001	1.01 (0.99–1.04)	0.362	–	–
sex (male)	3.47 (1.70–7.73)	0.001	3.03 (1.28–7.84)	0.016	3.04 (1.30, 7.78)	0.014
BMI	1.05 (0.99–1.12)	0.122	1.01 (0.92–1.10)	0.849	–	–
HT/CV	3.19 (1.74–5.97)	<0.001	2.35 (1.06–5.30)	0.036	2.75 (1.35, 5.72)	0.006
D	2.14 (1.00–4.54)	0.048	1.11 (0.43–2.79)	0.825	–	–
P/F	0.99 (0.98–0.99)	<0.001	0.99 (0.99–0.99)	<0.001	0.99 (0.99, 0.99)	<0.001
dyspnea	2.36 (1.30–4.35)	0.005	1.13 (0.51–2.45)	0.752	–	–
LUS score >20	6.44 (3.05–14.16)	<0.001	2.23 (0.85–6.00)	0.105	2.52 (1.01, 6.31)	0.046

OR: Odds Ratio; BMI: body mass index; HT/CV: hypertension/cardiovascular disease; LUS: lung ultrasound; ETI: endotracheal intubation; DNI: do not intubate order.
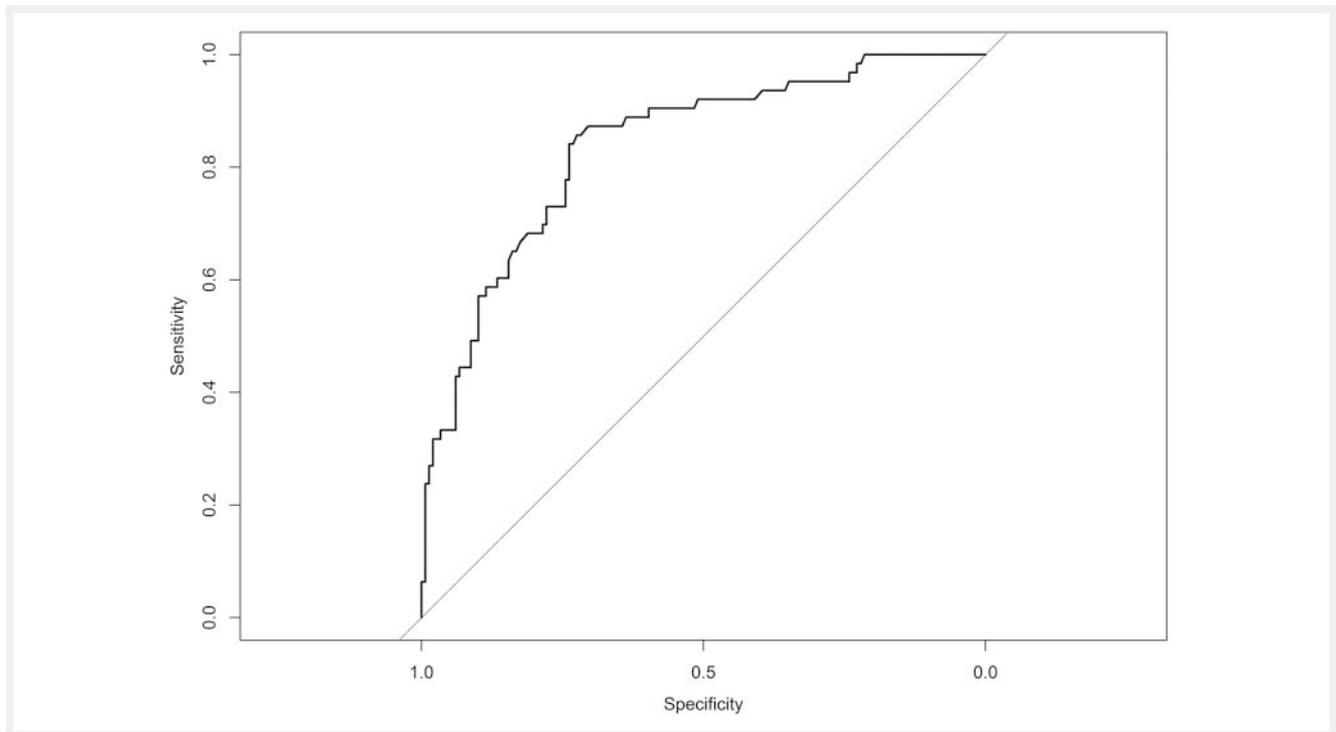
▶ **Fig. 1** Receiver operating curve analysis for primary outcome: After performing backward stepwise multivariable analysis, male sex (OR 3.04, 95 % CI 1.30–7.78, p 0.014), cardiovascular disease and hypertension (OR 2.75, 95 % CI 1.35–5.72, p 0.006), P/F(OR 0.99, 95 % CI 0.99–0.99 p < 0.001), and an LUS score >20 (OR 2.52, 95 % CI 1.01–6.31, p 0.046) were independent risk factors associated with primary outcome. Receiver operating characteristic (ROC) curve analysis was performed using a cut-off LUS score >20 and an AUC (area under the curve) of 0.837 was obtained.

Discussion

Our goal was to demonstrate how LUS could be an additional risk stratification tool in patients with COVID-19 pneumonia. From our data an LUS score >20 was an independent risk factor associated with the primary outcome (a composite of death, need for mechanical ventilation, and dispatch with no active further manage-

ment). Other independent risk factors were male sex, cardiovascular disease and hypertension, and P/F, while an LUS score <10 was an independent predictor for safe discharge from the ER along with age, BMI, and P/F. Even if the ROC curve is more powerful for the secondary outcome, it seemed most interesting to evaluate the use of LUS score in hospitalized patients. An increase in the LUS score in a patient throughout hospital stay can lead to

▶ **Table 4** Logistic regression analysis for the relationship between baseline clinical and LUS parameters to predict safe discharge from the ER.

	univariable analysis		multivariable analysis			
	OR	p-value	adjOR	p-value	adjOR	p-value
age	0.94 (0.91–0.97)	<0.001	0.97 (0.93–1.01)	0.152	0.96 (0.93–1.00)	0.073
sex (male)	0.49 (0.23–1.09)	0.079	1.17 (0.30–4.98)	0.820	0.87 (0.72–1.03)	0.13
BMI	0.76 (0.66–0.87)	<0.001	0.88 (0.71–1.06)	0.191	–	–
HT/CV	0.32 (0.12–0.74)	0.012	0.76 (0.18–3.12)	0.709	–	–
D	0.33 (0.05–1.19)	0.149	1.61 (0.14–13.61)	0.674	–	–
P/F	1.04 (1.03–1.05)	<0.001	1.03 (1.02–1.06)	<0.001	1.03 (1.02–1.05)	<0.001
dyspnea	0.21 (0.07–0.54)	0.003	0.47 (0.08–2.36)	0.376	–	–
LUS score < 10	32.33 (9.28–204.62)	<0.001	19.66 (3.25–379.78)	0.007	20.9 (3.51, 394)	0.006

OR: Odds Ratio; BMI: body mass index; HT/CV: hypertension/cardiovascular disease; LUS: lung ultrasound; ER: emergency room.
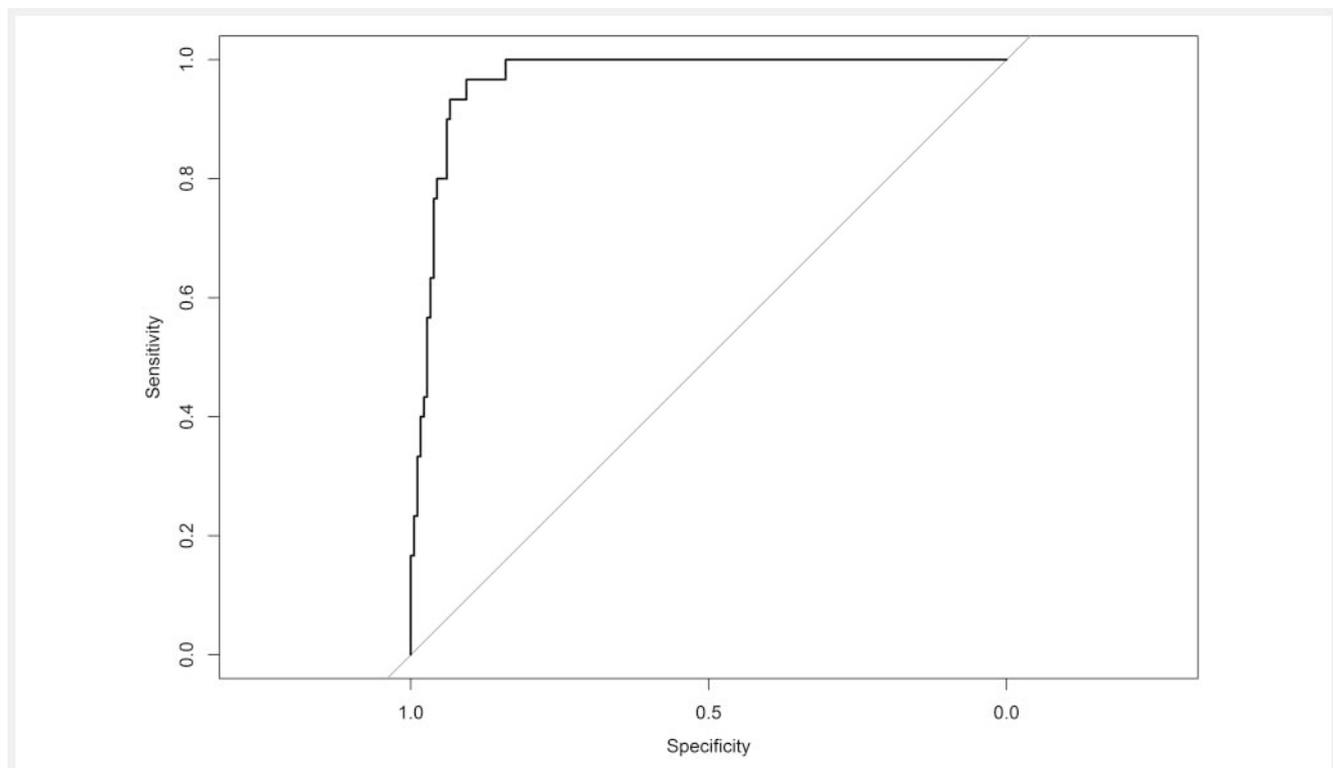
▶ **Fig. 2** Receiver operating curve analysis for secondary outcome: After performing backward stepwise multivariable analysis, age (OR 0.96, 95 % CI 0.93–1.00, p 0.073), BMI (OR 0.87, 95 % CI 0.72–1.03, p 0.13), P/F (OR 1.03, 95 % CI 1.02–1.05, p<0.001) and LUS score <10 (OR 20.9, 95 % CI 3.51–3.94, p 0.006) were independent risk factors associated with secondary outcome. Receiver operating characteristic (ROC) curve analysis was performed using a cut-off LUS score <10 and an AUC (area under the curve) of 0.967 was obtained.

the early recognition of clinical worsening and therefore to the correct identification of the right level of care. This can be crucial for the right access in intensive care units characterized by limited resources [16].

Ultrasound has proven to be an excellent tool for managing patients with COVID-19-related pneumonia and shows a good correlation with CT scan. In contrast with computerized tomog-raphy, ultrasound can be performed by a physician at bedside, thus minimizing the risk of contagion, and has no radiological hazard, which is of particular interest in pregnant and pediatric patients [18, 19]. Compared to chest X-ray, LUS is easier to per-form and shows higher sensitivity and specificity.

According to current clinical evidence, LUS patterns are repro-ducible in patients with COVID-19 pneumonia. The first pulmo-

nary manifestations are represented by a patchy distribution of interstitial artifactual signs (namely B lines). Subsequently, these patterns extend to multiple areas of the lung surface. Further evolution is characterized by evidence of patchy, small subpleural consolidations with associated areas of white lung. The evolution in consolidations, especially in a gravitational position, with or without air bronchograms, and their increasing extension along the lung surface indicate the evolution towards the phase of respiratory insufficiency that requires invasive ventilatory support [20].

LUS images of COVID-19 pneumonia are similar to those of other interstitial viral pneumonia and ARDS of a different origin. None of the LUS features seems to be COVID-specific, even if Volpicelli et al. has recently suggested the "light beam" as a typical sign of SARS-CoV-2 pneumonia [14], but during pandemic outbreaks, high clinical suspicion and high prevalence increase the pretest probability and LUS can contribute to early diagnosis of COVID-19 pneumonia. This potential benefit of LUS can be relevant in case RT-PCR swabs are not available or the time for processing specimens is considered excessively long, for the correct management of infected patients [21].

Performing LUS, we decided not to adopt the usual segmentation of the thorax conceived for ARDS in the ICU setting, because our patients were breathing spontaneously, and they could be evaluated while seated [22]. Our protocol uses a segmentation similar to that used in the emergency setting. We acquire 2 scans of the anterior segments (apical on midclavicular line and medial on the anterior axillary line) and only one in the lateral area. In fact, a single scan with a convex transducer, placed orthogonal to the medium axillary line proved to be adequate for the evaluation of the whole lateral segment in these patients. Since the disease typically involves the posterior lobes, we decided to divide this region in three different areas. As in the classic ARDS segmentation, it is important to have a limited number of scans and investigate the entire chest surface, which is possible with our segmentation method [23].

In the out-of-hospital setting, a score system for LUS assessment is an excellent tool for risk stratification of patients with SARS-COV-2 infection. Patients can be evaluated using a portable ultrasound machine and a pulse oximeter, considering oxygen saturation as a surrogate for PaO2 / FiO2 ratio.

Patients in our series were also assessed by echocardiography. Only a minority of patients (5.3 %) showed reduced contractility of the left ventricle. In regards to right ventricular evaluation, we found elevated values of TAPSE (median 24.5 mm [IQR 22–27]) and IVC collapsibility above 50 % in 82.6 % of patients.

There was no difference between the collapsibility index of patients with a less severe form (85 % with IVC collapsibility > 50 %) and the collapsibility index of patients in the primary outcome group (78.2 % with IVC collapsibility > 50 %).

This is the reason that the collapsibility index cannot be used as an indicator of negative prognosis. The IVC collapsibility index is likely to be differentiated in the two groups at a later date. In the case of worsening of respiratory exchange, the consequent reduction in cardiac contractility can lead to the reduction of TAPSE and to the transition from high collapsing IVC to fixed IVC.

The collapsing IVC appears to be in concordance with clinical types described by Gattinoni et al. In fact, Type 1 patients, who are characterized by severe hypoxemia associated with respiratory system compliance > 50 ml/cmH2O, are expected to create high negative intrathoracic pressure leading to a collapsing IVC, even in euvolemic patients without distributive or septic shock [24]. These findings deserve further research to understand the complex physiopathology of COVID-19 pneumonia.

This study has some limitations. First of all, patients enrolled in the study were not consecutive, since the decision to perform ultrasound was based on the presence of a trained doctor on duty. This may have reduced the statistical power of observations. However, the demographic and clinical characteristics of our cohort are similar to those reported in the published literature [25, 26].

Moreover, ultrasound is an operator-dependent technique and, given the retrospective nature of the study, it was impossible to check the intra-operator concordance. Finally, it is important to note that LUS can detect only a pathological process that extends in contiguity with the pleural line with the risk of not identifying severe pneumonia without peripheral involvement. Nevertheless, data from CT scan imaging of COVID-19 pneumonia revealed that pathological abnormalities involve the subpleural areas in most cases [27, 28].

However, despite these limitations, the possibility of stratifying patients with such a simple and immediate instrument like LUS seems plausible. It is probably more useful than X-ray and less demanding in economic, time, and risk terms than CT scan.

Dividing patients according to the date of symptom onset is of particular interest, especially when considering discharge from the ER. This was not possible in our study, due to the small sample size.

In our population 27 % of hospitalized patients had an LUS score < 10 at admission and 78 % of them did not use oxygen at all or needed only low flow oxygen with nasal prongs. The median number of days from symptom onset to ER admission was 5 days [IQR 3.5–7.5].

It seems reasonable to assume that a low LUS score is better in predicting a positive outcome when performed in a more advanced stage of the disease, between 6 to 11 days from symptom onset, whereas it could be less reliable when performed earlier.

Conflict of Interest

The authors declare that they have no conflict of interest.

Acknowledgements

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