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ARAŞTIRMA / RESEARCH

Effectiveness of the CLUE protocol in COVID-19 triage

COVID-19 triajında CLUE protokolünün etkinliği

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Abstract

Purpose: The purpose of this study was to evaluate the effectiveness of the CLUE protocol in COVID-19 triage.
Materials and Methods: Patients who presented to the emergency department due to dyspnea with oxygen saturation below 95 % and were diagnosed with COVID-19 by reverse transcription polymerase chain reaction (RT-PCR) tests were included in this prospective, observational study. Patients included in the study underwent lung ultrasound (LUS) in the light of the CLUE protocol, and were accordingly given LUS scores of between 0 and 36, also within the scope of the protocol. Patients were placed under observation, and clinical outcomes of discharge from the emergency department, admission to the ward, and admission to intensive care or discharge were recorded. ROC analysis was applied in the calculation of threshold values for LUS scores predicting discharge, admission to intensive care, and mortality.
Results: Forty-five patients with a mean age of 63 ± 18 years were included in the study. Fifteen patients (33 %) were treated on an outpatient basis and discharged, while 12 (27 %) were admitted to the ward and 18 (40 %) to the intensive care unit. Mortality occurred in 15 (33 %) patients. An LUS score lower than 3 was 97 % sensitive and 80 % specific for discharge, a score greater than 10 was 94 % sensitive and 78 % specific for admission to the intensive care unit, and a score higher than 11 was 93 % sensitive and 87 % specific for mortality. Based on regression analysis, an LUS score higher than 10 emerged as an independent risk factor for intensive care requirement, a score lower than 3 for discharge, and a score over 11 for mortality.
Conclusion: The CLUE protocol may be a useful bedside test in COVID-19 triage, and one that does not involve radiation or require laboratory tests.

Keywords: Triage, bedside ultrasound, COVID-19

Öz

Amaç: Bu çalışmanın amacı, CLUE protokolünün COVID-19 triajındaki etkinliğini değerlendirmektir
Gereç ve Yöntem: Bu prospektif, gözlemsel çalışmaya nefes darlığı nedeniyle acil servise başvuran oksijen saturasyonu %95' in altında olan ve revers transkripsiyon polimeraz zincir reaksiyonu (RT-PCR) testleri ile COVID-19 tanısı konan hastalar dahil edildi. CLUE protokolü doğrultusunda çalışmaya dahil edilen hastalara akciğer ultrasonu (LUS) uygulandı ve yine protokol kapsamında hastalara 0 ile 36 arasında değişen LUS skorları verildi. Hastalar takibe alındı ve acil servisten çıkış, servise yatış, yoğun bakıma yatış veya çıkış klinik sonuçları kaydedildi. Taburculuk, yoğun bakıma yatış ve ölümleri öngören LUS puanları için sınır değerlerinin hesaplanmasında ROC analizi kullanıldı.
Bulgular: Çalışmaya yaş ortalaması 63 ± 18 yıl olan 45 hasta dahil edildi. Hastaların 15' i (% 33) ayakta tedavi olmak üzere taburcu edildi, 12' si (% 27) servise, 18' i (% 40) yoğun bakım ünitesine yatırıldı. Toplam 15 (% 33) hastada ölüm meydana geldi. LUS puanının 3' ün altın olması taburculuk için % 97 duyarlı ve % 80 spesifik, 10' un üzerinde olması yoğun bakım ünitesine kabul için % 94 duyarlı ve % 78 spesifikti ve 11' in üzerinde olması mortalite için % 93 duyarlı ve % 87 spesifik olarak bulundu. Regresyon analizine göre LUS skorunun 10' un üzerinde olması yoğun bakım ihtiyacı için, 3' ün altında olması taburculuk için ve 11' in üzerinde olması ise mortalite için bağımsız bir risk faktörü olarak bulunmuştur.
Sonuç: CLUE protokolü, COVID-19 triajında radyasyon içermeyen ve laboratuvar testleri gerektirmeyen yararlı bir yatak başı testi olabilir.

Anahtar kelimeler: Triaj, yatakbaşı ultrason, COVID-19

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INTRODUCTION

Critical Corona Virus–19 disease (COVID-19) is particularly associated with pulmonary involvement and pneumonia capable of progressing to acute respiratory distress syndrome (ARDS)[1]. Patients must therefore be frequently assessed in terms of intensive care unit (ICU) requirements. Several scoring systems for evaluating severity of disease[2,3] and a number of thoracic computed tomography (CT) algorithms for assessing pulmonary involvement[4] have been developed. However, CT is not suitable for repeated use since it requires the patient to be moved to other areas and involves exposure to radiation[5]. Scoring generally relies on laboratory results, and calculation is therefore time-consuming. The use of bedside ultrasound, which does not require moving the patient or laboratory results and which does not involve exposure to ionizing radiation, for determining the severity of COVID-19 has therefore begun being considered.

Several studies have shown that bedside ultrasound can be used in the diagnosis and follow-up of critical patients[6]. Research has also shown that bedside lung ultrasound is useful in the diagnosis and follow-up of COVID-19 pneumonia[7,8]. As an indirect outcome of all these studies, Manivel et al. developed the COVID-19 Lung Ultrasound in Emergency Department (CLUE) protocol involving a lung scoring system (LUSS) based on pathological findings in point-of-care lung ultrasound (LUS) and assessment of patients in terms of oxygen requirement at the time of evaluation [9]. We think that the CLUE protocol will be a useful tool in the early recognition of critically ill patients when evaluating individuals with COVID-19 in the emergency department (ED). To the best of our knowledge, this is the first study to evaluate the use of the CLUE protocol as a triage tool for identifying critically ill patients in the ED.

The purpose of this study was to evaluate the success of the CLUE protocol in determining the severity of COVID-19 in the ED.

MATERIALS AND METHODS

Study design and setting

This prospective observational study was carried out between September 2020 and July 2021 in the ED of a tertiary hospital in Turkey receiving 450,000 annual ED visits. The ED in which the study was conducted has a monitorized critical patient care zone where critical patients with confirmed or suspected COVID-19 are followed-up, and an isolated area connected to the critical zone in which outpatients are followed-up. The study was performed in the isolated critical area set aside for COVID-19. An emergency medicine specialist, an emergency medicine resident, and two nurses work in the critical care area reserved for COVID-19 patients. Triage of these patients is performed by the emergency medicine specialist and the emergency medicine resident. Patients' vital signs and symptoms at the time of admission, information concerning comorbid diseases, and all physical examination findings are recorded onto patient charts. Ethical approval (no. 2020-KAE-0049) for the study was obtained from the İzmir Katip Çelebi University Clinical Trials Ethics Committee. Each patient or a relative thereof was informed in detail about the research and gave written consent to participate.

Study population

Adult patients presenting to the ED with dyspnea, with oxygen saturation lower than 95 %, and with COVID-19 confirmed by reverse transcription polymerase chain reaction (RT-PCR) tests were included in the study. Patients aged under 18, pregnant women, trauma patients, and patients with accompanying lung cancer or previously diagnosed decompensated heart failure were excluded. Patients who were intubated or developed cardiopulmonary arrest prior to LUS were also excluded.

Study protocol and data collection

Individuals' vital findings at time of presentation, demographic characteristics, and fingertip oxygen saturation levels were recorded onto case report forms. Bedside ultrasound was performed on all participants by a single qualified emergency medicine physician (A.Y) with 10 years' ultrasound experience using the recommended personal protective equipment. Bedside ultrasound was performed using a Mindray M5 portable ultrasound device with a 2-5 mHz convex probe in gray scale B mode at a depth of 13-15 cm. The device and probe were covered with protective gel for each patient, and the device was disinfected after each use. It was then allowed to dry before being used again. Point-of-care LUS was

performed with the patient in the seated position, and the findings were recorded onto the case forms. Patients' clinical outcomes were observed until discharge or exitus in the form of discharge from the emergency department, admission to the ward, admission to intensive care, or death. In case of patients re-presenting with the same disease, the outcome of the final presentation was employed in the analysis.

Lung ultrasonography assessment

The CLUE protocol developed by Manivel et al. was employed at point-of-care LUS evaluation[9]. The CLUE protocol involves the ultrasonographic evaluation of 12 regions, two anterior, two lateral, and two posterior, in each hemothorax. Each region was scored from 0 to 3. An LUS score of 0 describes a lung capable of containing one or two B-lines (Figure 1a), an LUS score of 1 more than two B lines and a thickened/irregular pleura (Figure 1b), an LUS score of 2 indicates confluent B-lines and subpleural consolidation < 1 cm (Figure 1c), and an LUS score of 3 indicates subpleural consolidation > 1 cm and/or air bronchograms or vascularity (Figure 1d). Total possible scores range between 0 and 36, with a score of 0 being regarded as normal, scores of 1-5 as mild pulmonary involvement, 6-15 as moderate pulmonary involvement, and above 15 as severe involvement[1].

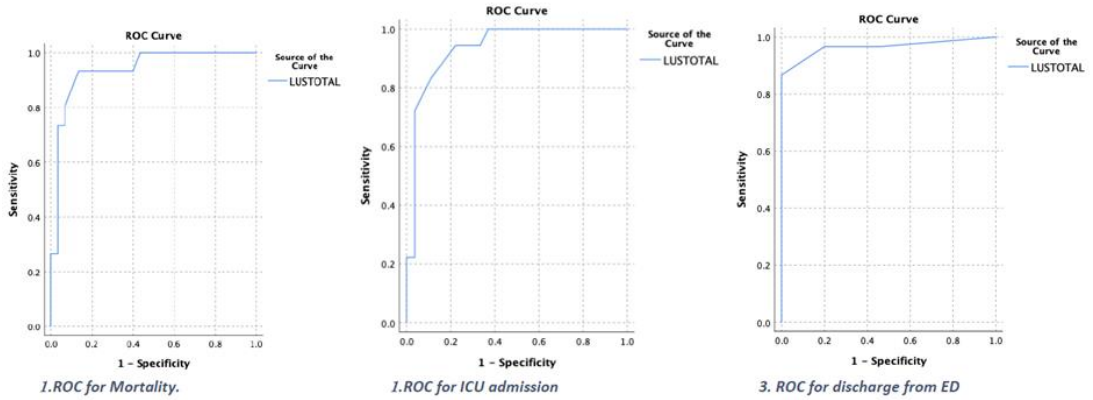

Figure 1. ROC curves for mortality, ICU admission and discharge from ED

Statistical analysis

MedCalc version 19.0.7 (MedCalc Software bvba, Belgium) was used to calculate the sample size and study power. When the effect value was adopted as 0.5 with a 95 % confidence interval and 5 % error, the minimum number of patients required for inclusion in the study was 54. The study was eventually completed with 65 patients. At post-hoc analysis, LUS exhibited a 0.05 alpha error and predictive power (1-b err prob) of 99 % for both in-hospital mortality and ICU requirement. Data analysis was performed on SPSS 26 (IBM SPSS Statistics for Macintosh, version 27.0) software. The significance level of the tests was set at $p < 0.05$. Frequency distributions (number and percentage) were given for categorical variables and descriptive statistics (mean, standard deviation, median, and interquartile range) for numerical variables. Homogeneity (Levene's test) and normality (Shapiro-Wilk test) results were used to decide on the statistical methods employed in comparing the study groups. ROC analysis was performed to evaluate the success of LUS in predicting mortality, ICU admission, and discharge from the ED. Data were rendered categorical using cut-off values obtained from the ROC analysis. Binary logistic regression analysis was applied to evaluate the success of LUS using categorical data. The regression analysis results were expressed as Odds Ratio (OR) and Nagelkerke model success. All data were expressed at a 95 % confidence

interval. p values < 0.05 were regarded as statistically significant.

RESULTS

Forty-five patients diagnosed with COVID-19 were included in the study. A work-flow chart describing the exclusion and inclusion procedures is shown in Figure 2. The patients' mean age was 63 ± 18 years, and 27 (60 %) were men. The patients' demographic characteristics are shown in Table 1. ROC analysis applied to determine the success of LUS scores in predicting mortality, admission to the ICU, and discharge from the ED revealed that a score of 11 or more was significant for mortality, a score of 10 or more was significant for admission to the ICU, and a score of 3 or less was significant for discharge from the ED (Table 2). ROC curves obtained from the ROC analysis are shown in Figure 1.

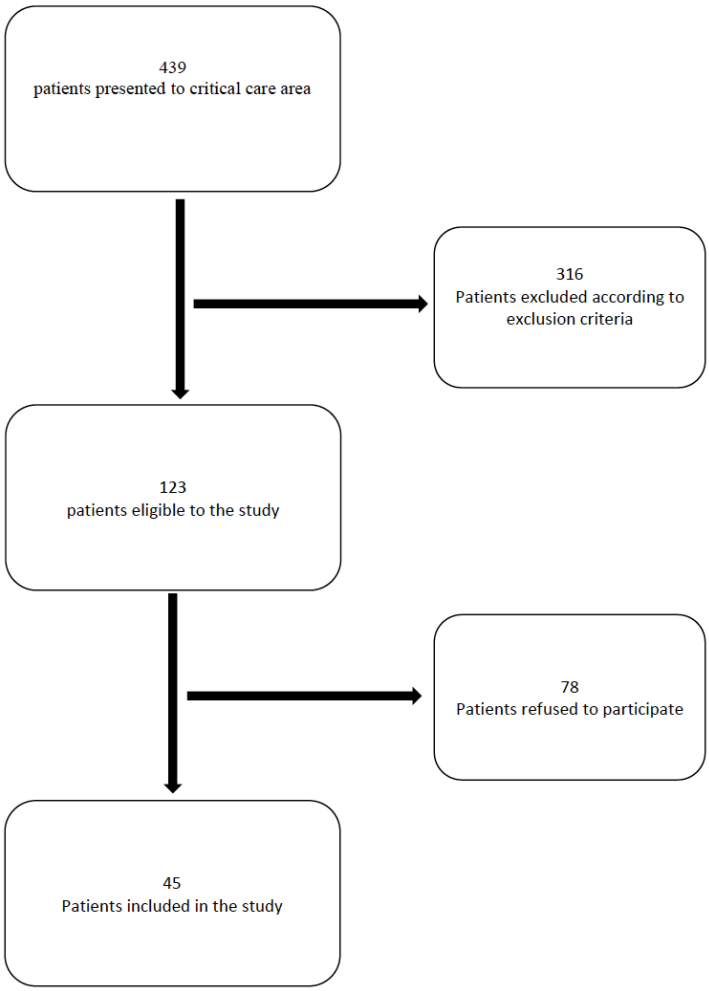

Figure 2. Work-flow chart

Tablo 1. Demographic characteristics of subjects

Paramaters		**Number (%)**
Clinical Outcome	Discharged	15 (% 33)
	Ward admission	12 (27 %)
	ICU	18 (40 %)
	Total	45 (100)
LUS score	0	9 (20 %)
	1	8 (18 %)
	2	15 (33 %)
	3	13 (29 %)
	Total	45 (100 %)
Mortality	No	30 (67 %)
	Yes	15 (33 %)
	Total	45 (100 %)
Comorbid disease	No	10 (22 %)
	Yes	35 (78 %)
	Total	45 (100 %)

ICU: Intensive care unit, LUS: Lung ultrasound

Table 2. ROC analysis results presenting the success of LUS in predicting mortality, ICU hospitalization and discharge from ED

	Cut-off	**AUC**	**Sensitivity (95 % CI)**	**Specificity (95 % CI))**	**PPV (95 % CI)**	**NPV (95%CI)**	**P**
Mortality	11	0.939	93 (% 68- 100)	87 (% 69-96)	78 (% 58-90)	96 (% 79-99)	<0.001
ICU admission	10	0.935	94 (% 73-100)	78 (% 58-91)	74 (% 58-85)	95 (% 76-99)	<0.001
Discharge from ED	3	0.966	87 (% 60-98)	93 (% 78-99)	87 (% 63-96)	93 (% 79-98)	<0.001

LUS: Lung ultrasoun, ICU: Intensive care unit, AUC: Area under the curve, ED: Emergency department, PPV: Pozitive predictive value, NPV: Negative predictive value

Table 3. Univariate Regression analysis evaluating the success of LUS in predicting mortality, ICU admission and discharge from ED

			95 % CI for OR	
	P	**OR**	**Lower**	**Upper**
Mortality	<0.001	91	9.256	894.673
ICU admission	<0.001	59.5	6.518	540.183
Discharge from ED	<0.001	91	11.513	719.228

LUS: Lung ultrasoun, ICU: Intensive care unit, AUC: Area under the curve, ED: Emergency department, OR: Odds ratio, CI: Confident interval

Univariate regression analysis was applied to assess how successful LUS scores were in predicting mortality, ICU admission, and discharge from the ED. This showed that LUS scores of 11 or more were significant for mortality, scores of 10 or more for admission to the ICU, and scores of less than 3 for discharge from the ED (OR:91, OR:59.5, OR:91 respectively) (Table 3). Analysis of the univariate regression models revealed that LUS alone explained 67 % of all deaths according to Nagelkerke, 59 % of all admissions to the ICU, and 69 % of all discharges from the ED.

DISCUSSION

Pulmonary involvement is the principle predictor of a threshold point and severe involvement in COVID-19[10]. Patients therefore need to be assessed in terms of pulmonary involvement in order to decide on the severity of the disease during triage in the ED. This study tested the effectiveness of the CLUE protocol

among bedside ultrasound protocols developed in order to evaluate the severity of COVID-19. The CLUE protocol emerged as an effective protocol not involving exposure to radiation or requiring laboratory results in COVID-19 triage.

In the CLUE protocol developed by Manivel et al. for assessing the severity of COVID-19 disease, total scores of 1-5 indicate mild severity, 5-15 moderate severity, and more than 15, severe disease. However, it leaves the final decision regarding whether LUS scores are sufficient for deciding on admission to the ward and the ICU and discharge up to the clinician[9]. In the present study, rather than classifying cases as mild, moderate, or severe, as in the CLUE protocol, the same ultrasound findings were used to decide on discharge, or admission to the ward or the ICU. LUS scores lower than 3 were found to be significant in terms of discharge, and scores over 10 emerged as significant in terms of admission to the ICU. Although our results were similar, we think that the difference derived from variations in clinical outcomes.

The second important finding in the present study is that LUS scores were tested as a marker of mortality, and scores above 11 emerged as significant from that perspective. Manivel et al. established no direct association between LUS scores and mortality[9]. Subsequently, however, in a study involving patients hospitalized due to COVID-19, Linchtel et al. suggested that an LUS score above 18 was significant in terms of mortality. However, only hospitalized patients were enrolled in that study, while outpatients were not included. We think that this explains the higher LUS score cut-off value reported by those authors for predicting mortality than that in the present study [11]. Ji et al. included patients with a similar LUS score range to that in our study population, reporting an LUS score higher than 12 as a high risk and associated with mortality, with a cut-off value also similar to that in the present study[12].

Various severity and early warning scoring systems have been investigated for the management of COVID-19, and the success of a number of parameters in determining clinical outcomes has been evaluated. For example, Pokeerbux et al. assessed the success of the National Early Warning Score (NEWS) in determining intensive care admission and in-hospital mortality in patients with COVID-19. Those authors reported an OR of 3.78 for admission to the ICU and an OR of 6.11 for mortality[13]. Liang et al. identified chest radiography abnormality, age, hemoptysis, dyspnea, unconsciousness, number of comorbidities, cancer history, neutrophil-to-lymphocyte ratio, lactate dehydrogenase, and direct bilirubin as predictive factors in determining the severity of COVID-19 (OR values between 1.00 and 4.71)[14]. Arminanzas et al. described the quick sequential organ failure assessment (quick SOFA) and COVID-GRAM score as predictive factors for the development of severe disease, with OR values of 0.65 and 9.40, respectively[15]. Zhou et al. showed that thoracic CT scores were effective in estimating disease prognosis (OR: 6.88)[2]. In the present study, LUS scores emerged as an independent predictor of mortality (OR: 91), admission to intensive care (OR: 59.5), and discharge from the ED (OR: 91), and as more effective than all other scoring systems. In addition, many scoring systems employed in other studies are dependent on laboratory results, while LUS offers the advantages of yielding rapid results, and being a simple and non-invasive marker.

The principal limitations of this study are its single-center nature and relatively low patient number. Further multi-center studies with more patients are now needed. In addition, since individuals with acute heart failure and lung cancer were not included, the results cannot be applied to these patients. Another limitation is that although the operator applying the ultrasound was blinded to the patient's vital findings, laboratory findings, and pulmonary imaging data, the operator was not blinded to the patient's general condition or inspection data such as the presence or absence of dyspnea. This may have allowed the operator to form a crude idea of the patient's general condition, and naturally poses a limitation on the study.

The CLUE protocol may be an effective, simple, and rapid method in COVID-19 triage and in predicting mortality. This now needs to be tested in larger patient populations. Future studies might usefully be planned in which the CLUE protocol is compared with other methods in the triage of patients with COVID-19.

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