DOI: 10.7860/JCDR/2024/63123.19219

Prevalence of Exercise-induced Desaturation in Survivors of Severe COVID-19 Pneumonia and the Predictive Value of Lung Ultrasound: A Cross-sectional Study

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ABSTRACT

Introduction: Survivors of severe Coronavirus Disease-2019 (COVID-19) pneumonia may experience Exercise-Induced Desaturation (EID), which can remain undiagnosed at discharge, as most exhibit normal resting Arterial Blood Gases (ABGs). This undiagnosed condition may lead to unexpected hospital readmissions, causing additional burden to the health system. However, the prevalence of EID among this population, especially in developing countries, is not well documented.

Aim: To estimate the prevalence of EID among survivors of severe COVID-19 pneumonia and to explore the predictive role of Lung Ultrasound Scan (LUS) in detecting EID.

Materials and Methods: This hospital-based, observational, cross-sectional study was conducted at the Institute of Chest Diseases in Kozhikode, Kerala, India from October 2021 to September 2022. It involved 153 COVID-19 patients aged 18 years and above who had recovered from severe pneumonia, were otherwise fit for hospital discharge, and had normal resting ABGs. The study examined the prevalence of EID using the 6-Minute Walk Test (6MWT). Additionally, it investigated the predictive ability of a LUS for EID. A LUS was performed on all patients and scoring was conducted according to the established protocol.

Results: The mean age of the study subjects was 53.50±14.13 years, with 119 (77.8%) being male. During the 6MWT, 96 patients (62.7%) showed significant desaturation. A total of 83 (95.4%) subjects in the desaturated group required Non-Invasive Ventilation (NIV) compared to 4 (4.6%) in the non-desaturated group ($p<0.001$). All 24 (100%) subjects in the desaturated group required Invasive Mechanical Ventilation (IMV), while none in the non-desaturated group did. The mean Length Of Stay (LOS) in the hospital was 35.50±13.35 days for the desaturated group, compared to 23.32±16.25 days for the non-desaturated group ($p<0.001$). The LUS score was significantly higher in the desaturated group (16.61±5.92) than in the non-desaturated group (5.54±4.62). The Receiver Operating Characteristic (ROC) curve for the LUS score indicated a cut-off value of 8.5 for identifying significant EID.

Conclusion: Survivors of COVID-19 who recovered from Acute Respiratory Failure (ARF) and have normal resting ABGs may still have significant EID. A protocol-based LUS score can potentially identify individuals at risk for EID.

Keywords: Acute respiratory failure, Coronavirus Disease-2019, Lung ultrasound scan score, Six-minute walk test

INTRODUCTION

The SARS-Coronavirus 2 (SARS-CoV-2) is a highly transmissible and virulent virus that has had a significant impact on global public health and caused considerable disruption to daily life [1]. Approximately 14% of infected individuals develop severe pneumonia, with around 5% experiencing critical manifestations [2]. In a country like India, with a population of more than 1.4 billion, these percentages represent enormous numbers. Recovery from ARF in patients hospitalised for COVID-19 is often assessed by the normalisation of saturation as measured by a pulse oximeter, or preferably by normalisation of ABG. Even long after hospital discharge , a significant proportion of these patients report persistence of breathlessness, especially on exertion [3].

There is evidence that radiological findings persist after hospital discharge. One recent study showed that 94% of patients who recovered from COVID-19 pneumonia had residual findings on a Computerised Tomography (CT) scan. The most common CT manifestation was bilateral Ground-Glass Opacity (GGO) with a subpleural distribution [4]. Another study indicated that a quarter of COVID-19 patients still had persistent opacities on a CT scan at a three-month follow-up after discharge. In the same study, the diffusing capacity of the lung for carbon monoxide (DLCO) was below the lower limit of normal in 24% [5]. Reduced DLCO is well described as a cause for EID. Although literature on Covid-19 is enormous, the prevalence of EID in this group of patients , who were otherwise fit for discharge, and its correlation with LUS score has not been adequately researched, except in a few studies [3,6]. The utility of lung ultrasound in COVID-19 has been extensively studied [7], yet the correlation of LUS with the prevalence of EID has not been adequately represented in the literature [3]. This issue is particularly important in developing countries, where re-admissions related to persistent EID could further strain an already overburdened health system [8]. The COVID-19 pandemic has witnessed a scarcity of both intensive care and non-intensive care beds, as well as medical resources, including oxygen and life-saving medications. In this context, preventing every possible readmission is crucial. This study, which sheds light on this aspect, is both pertinent and under-researched. The correlation between LUS findings and EID also helps to easily triage these patients, especially since the lung abnormalities in severe COVID-19 are predominantly peripheral [9].

The aim of this study was to investigate the prevalence of EID in patients showing normal ABG values at rest after recovery from COVID-19 pneumonia, who were otherwise fit for discharge. The study also explored the predictive role of LUS in detecting EID as a secondary outcome.

MATERIALS AND METHODS

This was an observational, cross-sectional, hospital-based study conducted in the Department of Pulmonary Medicine at the

Institute of Chest Diseases, Kozhikode, Kerala, India. It enrolled consecutive patients from October 2021 to September 2022. The study received approval from the Institutional Human Ethics Committee (GMCKKD/RP2021/IEC/258).

Inclusion criteria: Patients aged 18 years and above, who were Severe Acute Respiratory Syndrome- Coronavirus-2 Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) positive from nasopharyngeal or oropharyngeal swabs, had recovered from severe pneumonia (with normal ABGs), and were otherwise fit for hospital discharge as per hospital protocol, were included in the study.

Exclusion criteria: Subjects with concomitant neurological or orthopaedic diseases, or any significant cardiorespiratory diseases that could compromise the 6MWT results, were excluded from the study.

Sample size estimation: The study required a sample size of 153 patients to estimate the expected proportion with an 8% absolute precision and a 95% confidence interval. This was based on a similar study conducted in Italy, which found the prevalence of EID in survivors of severe COVID-19 pneumonia to be 43% [3].

Procedure

Socio-demographic and other clinical variables were recorded, including the need for mechanical ventilation, Length of stay (LOS) in the Intensive Care Unit (ICU) and ward, using a proforma. All participants underwent a formal cardiology evaluation with echocardiography. The study provided necessary safeguards for participants and staff in accordance with hospital protocols. A portable LUS machine (5 MHz curved transducer, Mindray Investment Co., Ltd.) was exclusively available for the study. A pulmonologist with over five years of experience in lung ultrasonography performed the LUS, following the standardised approach proposed by Soldati G et al., [10]. Fourteen quadrants were scanned along the paravertebral, midaxillary, and midclavicular lines, including three posterior, two lateral, and two anterior areas on either side.

Quadrants 1, 2, and 3 were located along the paravertebral line above the curtain sign, at the inferior angle of the scapula, and at the spine of the scapula, respectively. Quadrants 4, 5, and 6 corresponded to areas on the left side. Quadrants 7, 8, and 9, 10 were along the midaxillary line below and above the nipple line on the right and left sides, respectively. Quadrants 11 and 12 were on the right midclavicular line above and below the inter nipple line, with 13 and 14 as the corresponding areas on the left side. LUS scoring for each quadrant (scores 0 to 3) was performed, and the scores were summed to obtain a final score (0 to 42).

Scoring Protocol [10,11]:

Score 0-The pleural line is regular and continuous with A-lines present.

Score 1-The pleural line is indented with vertical areas of white lung visible.

Score 2-The pleural line is fragmented, with small to large areas of consolidation and vertical areas of white lung beneath the consolidated area.

Score 3-Dense and extensive vertical areas of white lung are present, with or without consolidation.

Subsequently, the 6MWT was performed according to the ATS guidelines by a respiratory therapist, under the close supervision of a pulmonologist [11]. Pre and post-procedure clinical data were noted. Patients were classified as "desaturators" if they showed a drop in oxygen saturation of ≥4% during the 6MWT, and the remaining patients were labeled as "non-desaturators" [12]. The 6MWT was conducted after LUS scoring to prevent any bias.

STATISTICAL ANALYSIS

All collected data were coded and entered into a Microsoft excel sheet, which was double-checked and analysed using Statistical Package for Social Sciences (SPSS) version 22.0. Quantitative variables were summarised using means and Standard Deviation (SD). Categorical variables were represented using frequencies and percentages. An independent sample t-test was used to test the statistical significance of differences between the means of variables among different independent groups. The Pearson Chi-square test and Fisher's-exact test were used for comparing categorical variables between groups. ROC curves were generated for the distance covered in the 6MWT and the lung ultrasound score to determine the diagnostic characteristics for predicting significant desaturation. A p-value of less than 0.05 was considered statistically significant.

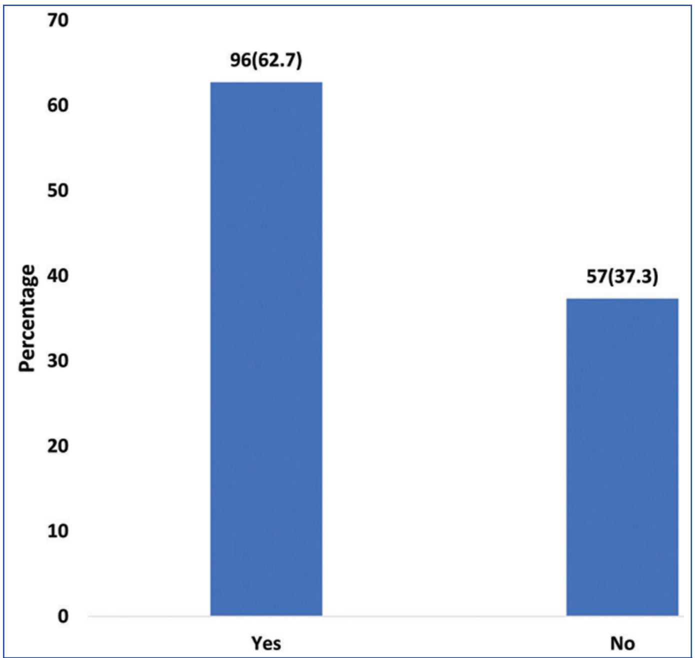
RESULTS

One hundred fifty-three (153) subjects meeting the enrollment criteria were consecutively recruited into the study. The mean age of the study population was 53.50 (±14.13) years, with 119 (77.8%) being male. Demographic and clinical data are depicted in [Table/Fig-1]. The mean age of the desaturator group was 57.73 (±10.98) years and that of the non-desaturators was 46.37 (±15.96) years (p<0.001). Among the desaturators, 90 (75.6%) were male, and in the non-desaturator group, 29 (24.4%) were male (p<0.001). The mean Body Mass Index (BMI) of the study population was 24.13

Demographic Parameters	Overall N=153	Desaturators N=96	Non-desaturators N=57	p-value
Age[$]	53.50±14.13	57.73±10.98	46.37±15.96	**<0.001***
Male[@]	119 (77.8)	90 (75.6)	29 (24.4)	**<0.001***
BMI[$]-kg/m²	24.13±4.83	23.60±3.14	25.02±6.74	0.079
Co-morbidities				
Diabetes mellitus[@]	59 (38.6)	51 (86.4)	8 (13.6)	**<0.001***
Hypertension[@]	55 (35.9)	40 (72.7)	15 (27.3)	0.056
Chronic renal failure[#]	13 (8.5)	10 (76.9)	3 (23.1)	0.373
CAD[@]	24 (15.7)	18 (75)	6 (25)	0. 176
Clinical parameters				
NIV use[@]	87 (56.9)	83 (95.4)	4 (4.6)	**<0.001***
IMV[@]	24 (15.7)	24 (100)	0 (0)	**<0.001***
LOS ICU[$] (days)	9.07±9.45	12.23±9.29	3.75±7.09	**<0.001***
LOS total[$] (days)	30.96±15.61	35.50±13.35	23.32±16.25	**<0.001***
6MWT				
Distance covered[$] (m)	278.89±148.27	191.13±105.26	426.70±73.73	**<0.001***
Rest SpO_2 value[$]	95.33±1.82	94.52±1.63	96.70±1.23	**<0.001***
Nadir SpO_2 value[$]	88.08±5.97	84.03±3.28	94.91±1.71	**<0.001***
Resting HR[$]	82.97±10.78	83.15±9.50	82.67±12.74	0.792
Maximum HR[$]	103.71±17.78	109.49±15.24	93.96±17.60	**<0.001***
Initial RR[$]	22.15±4.21	24.29±2.72	18.54±3.81	**<0.001***
Final RR[$]	33.32±8.72	38.15±5.88	25.19±6.37	**<0.001***
LUS[$]	12.49±7.65	16.61±5.92	5.54±4.62	**<0.001***

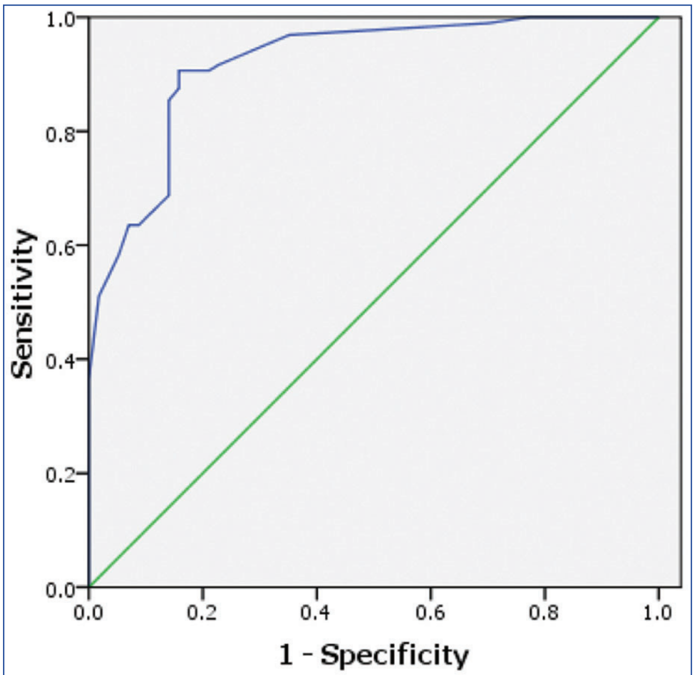
[Table/Fig-1]: Demographic and clinical characteristics of desaturators and non-desaturators.
Variables are expressed as mean (SD) or percentage (%); BMI: Body mass index; CAD: Coronary artery disease; NIV: Non-invasive ventilation; IMV: Invasive mechanical ventilation; LOS: Length of stay; 6MWT: Six minute walk test; SpO_2: Pulse oximetry; HR: Heart rate; RR; Respiratory rate; LUS: Lung ultra sound; *statistically significant
[@]Chi-square test; [#]Fisher's-exact test; [$]Independent sample t-test

(±4.83); for the desaturator group it was 23.60 (±3.14), and for the non-desaturator group, it was 25.02 (±6.74) (p=0.079). No statistically significant differences were observed between the groups regarding co-morbidities,, except for diabetes mellitus (p<0.001). After conducting the 6MWT, it was found that out of 153 participants, 96 (62.7%) showed EID [Table/Fig-2].



[Table/Fig-2]: The prevalence of significant desaturation in the study population.

In terms of treatment for ARF, 87 (56.9%) received NIV, while 24 (15.7%) required IMV with the frequency of their use differing significantly between the two groups. In the desaturator group, the mean nadir SpO_2 (%) was 84.03±3.28 compared to 94.91±1.71 in the non-desaturator group, a difference that was statistically significant (p<0.001). The desaturator group had a significantly higher LUS score than the non-desaturator group (12.23±9.29 vs 5.54±4.62; p<0.001). From the ROC curve [Table/Fig-3], the best cut-off value of LUS for discriminating desaturators from non-desaturators during the 6MWT was 8.50, with a sensitivity of 0.90 and a specificity of 0.84, and an Area Under the ROC Curve (AUC) of 0.920 with a 95% CI (0.876-0.963).



[Table/Fig-3]: ROC curve of lung ultra sound score for predicting significant desaturation.
AUC=0.920

DISCUSSION

This study highlights that patients recovering from severe COVID-19 pneumonia can still experience EID even if they have normal ABGs at rest, indicating the need for further evaluation.

Few studies have examined the relationship between standardised walking tests and LUS in patients who have survived severe COVID-19 pneumonia [3]. This current study found a higher prevalence of EID (62.7%) compared to a similar study by Carlucci A et al., which reported that up to 43% of the sample had EID [3]. The study was conducted in a referral center for critically ill patients in northern Kerala, which might account for the higher incidence of EID. Among the co-morbidities, diabetes mellitus showed a significant difference between the desaturator and non-desaturator groups. The use of mechanical ventilation also revealed a significant difference between the two groups, whereas a similar study reported no difference [3]. This discrepancy may be due to the higher proportion of critically ill subjects in the present study population. Total Length of Stay (LOS), as well as ICU LOS, differed significantly between the groups, which is consistent with similar studies [3].

This could be due to the higher likelihood of mechanical ventilation use in the desaturator group. Resting SpO_2, nadir SpO_2, resting, and maximum heart rate during the 6MWT also showed significant differences between the two groups. Except for the resting SpO_2 value, these findings were comparable to other studies [3]. Multivariate analysis revealed diabetes mellitus and maximum heart rate to be non-significant. Contrary to the comparable study, our study found a significant difference in the distance covered during the 6MWT between the two groups [3]. The increased number of re-admissions during the COVID-19 pandemic could be attributed to persistent EID, suggesting that similar, larger studies could lead to a policy change in the management of severe COVID-19 pneumonia.

A median LUS score greater than or equal to 8.5 was shown to accurately predict EID in the present study. Carlucci A et al., found a similar value [3]. During the COVID-19 pandemic, the predictive accuracy of LUS was researched and found to be beneficial. A higher LUS score was associated with greater pneumonia severity [13]. A LUS greater than 14 is linked to worse outcomes [14]. A recent systematic review showed a 40% reduction in DLCO in post-infection COVID-19 patients [15]. However, access to a pulmonary function testing facilities can be practically challenging during the COVID-19 pandemic. Although the 6MWT is an easy, simple, and inexpensive test that provides useful information on submaximal exercise capacity, its execution requires a corridor of about 20 to 30 meters [16].

More importantly, the study subjects need to be mobilised to the site, which becomes all the more difficult during a pandemic. Ultrasound has now become ubiquitous in ICUs across the globe, and its utility for diagnosis and monitoring has increased markedly [17]. It is now increasingly used by emergency and critical care professionals as well as pulmonologists [18]. Therefore, wherever an ultrasound machine and expertise are available, it will be helpful to triage severe COVID-19 pneumonia survivors who have significant EID. Those with significant EID may eventually require a pulmonary rehabilitation program or prolonged clinical follow-up. There are few studies available in the literature addressing this pertinent issue, and this study has attempted to fill the knowledge gap.

Limitation(s)

First, the research was conducted in a tertiary care referral center dedicated to severe COVID-19 cases in northern Kerala. The majority of patients were critically ill and required mechanical ventilation. Consequently, the study population may have been biased towards more severe cases. Second, due to the protocol followed at the institution, Computerised Tomography Pulmonary Angiography

(CTPA) was not performed in most of the patients. Therefore, the prevalence of concurrent pulmonary thromboembolism in the study population remains unclear.

CONCLUSION(S)

The prevalence of EID was as high as 62.7% among COVID-19 patients who had recovered from severe pneumonia. A LUS score of 8.5 or higher may be used to reliably predict those who significantly desaturate, allowing for further clinical evaluation and referral to a pulmonary rehabilitation program. Further large-scale prospective research may be needed to validate the effectiveness of the LUS score threshold for forecasting EID, as COVID-19 is expected to persist for an extended period with the potential for intermittent pandemic waves.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Feb 04, 2023
- Manual Googling: May 18, 2023
- iThenticate Software: Dec 26, 2023 (12%)

ETYMOLOGY: Author Origin

EMENDATIONS: 7

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Feb 01, 2023**
Date of Peer Review: **Apr 17, 2023**
Date of Acceptance: **Dec 30, 2023**
Date of Publishing: **Apr 01, 2024**