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Original Article

The novel use of diaphragmatic excursion on hospital admission to predict the need for ventilatory support in patients with coronavirus disease 2019

Mina Adolf Helmy, Lydia Magdy Milad, Ahmed Hasanin *, Maha Mostafa

Department of Anaesthesia and Critical Care Medicine, Cairo University, Cairo, Egypt

A B S T R A C T

Background: We aimed to evaluate the ability of diaphragmatic excursion at hospital admission to predict outcomes in patients with coronavirus disease-2019 (COVID-19).

Methods: In this prospective observational study, we included adult patients with severe COVID-19 admitted to a tertiary hospital. Ultrasound examination of the diaphragm was performed within 12 h of admission. Other collected data included peripheral oxygen saturation (SpO_2), respiratory rate, and computed tomography (CT) score. The outcomes included the ability of diaphragmatic excursion, respiratory rate, SpO_2, and CT score at admission to predict the need for ventilatory support (need for non-invasive or invasive ventilation) and patient mortality using the area under the receiver operating characteristic curve (AUC) analysis. Univariate and multivariable analyses about the need for ventilatory support and mortality were performed.

Results: Diaphragmatic excursion showed an excellent ability to predict the need for ventilatory support, which was the highest among respiratory rate, SpO_2, and CT score; the AUCs (95% confidence interval [CI]) was 0.96 (0.85–1.00) for the right diaphragmatic excursion and 0.94 (0.82–0.99) for the left diaphragmatic excursion. The right diaphragmatic excursion also had the highest AUC for predicting mortality in relation to respiratory rate, SpO_2, and CT score. Multivariable analysis revealed that low diaphragmatic excursion was an independent predictor of mortality with an odds ratio (95% CI) of 0.55 (0.31–0.98).

Conclusion: Diaphragmatic excursion on hospital admission can accurately predict the need for ventilatory support and mortality in patients with severe COVID-19. Low diaphragmatic excursion was an independent risk factor for in-hospital mortality.

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Introduction

Coronavirus disease-2019 (COVID-19) has emerged in China and has spread worldwide, producing an aggressive pandemic with > 3 million deaths. The overwhelming surge of patients in a short period of time results in an unusual load that exceeds the capacity of the critical care units and, sometimes, the collapse of the healthcare system in some countries [1,2]. One of the important points to mitigate the severity of the outbreak is proper triaging and early detection of patients with more severe illness to prioritise those who require high dependency units. During the surge of COVID-19 cases, there was a shortage of mechanical ventilators and intensive care unit (ICU) beds [3]; hence, it is important to identify patients at higher risk for ventilatory support as early as possible.

Despite the acceptable accuracy of several laboratory parameters and computed tomography (CT) in risk stratification of patients with COVID-19 [4,5], routine CT imaging is sometimes time and effort-consuming and carries the risk of spreading infection inside hospitals. Laboratory investigations may sometimes not be available when resources are limited.

The diaphragm is the main respiratory muscle and is responsible for the majority of the inspiratory drive [6]. Diaphragmatic dysfunction is frequently observed in patients with respiratory failure and has been associated with an increased risk

* Corresponding author at: Faculty of Medicine, Cairo University, Cairo, Egypt.
  E-mail address: ahmedmohamedhasanin@gmail.com (A. Hasanin).

of failure of weaning from mechanical ventilation [6–8]. Early diaphragmatic dysfunction occurs in nearly 60% of critically ill patients and is associated with increased mortality [9]. Early diaphragmatic dysfunction is explained by high levels of circulating pro-inflammatory cytokines and oxidative stress [9]. COVID-19 is characterised by an excessive host inflammatory response with a surge in cytokine levels [10]. Hence, diaphragmatic dysfunction is expected in such patients. In patients with COVID-19, diaphragmatic dysfunction was reported to be able to predict non-invasive ventilation failure [11] and weaning failure [12] in patients receiving ventilatory support. In this study, we hypothesised that evaluation of diaphragmatic function in patients with severe COVID-19 early after hospital admission could identify high-risk patients for ventilatory support and mortality.

This study aimed to evaluate the ability of diaphragmatic excursions assessed within 12 h after admission to predict the need for ventilatory support and mortality in patients with severe COVID-19.

Patients and methods

This prospective observational study was conducted in the ICU of a tertiary hospital after approval from the institutional Research Ethics Committee (N-50-2021) and a written informed consent form was obtained from the participants or their next-of-kin. We consecutively included adult (> 18 years) patients admitted to the ICU with severe COVID-19 infection according to the World Health Organization criteria (peripheral oxygen saturation [SpO_2] < 94%, arterial oxygen pressure/fraction of inspired oxygen (PaO_2/FiO_2) ratio < 300, respiratory rate > 30 breaths/min, haemodynamic instability) and confirmed positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by reverse-transcriptase polymerase chain reaction. Exclusion criteria included patients admitted to the ICU for > 12 h, patients who received ventilatory support early on admission, patients with diaphragmatic paralysis, neuromuscular disease, or pre-existing lung pathology (*e.g.*, lung tumour or metastasis).

The admitted patients were treated according to our standardised protocol for respiratory and haemodynamic support [13,14]. Initially, patients received oxygen through a facemask, and oxygen flow was adjusted to maintain a SpO_2 of 92–96%. If the respiratory rate did not fall below 30 breaths/min and/or SpO_2 did not reach the target despite oxygen therapy then awake proning, non-invasive ventilatory support was initiated (in the form of high-flow nasal oxygen, that was escalated to non-invasive mechanical ventilation) [15]. Patients received invasive ventilation if non-invasive ventilation was considered failure (SpO_2 < 90%, respiratory rate > 35 breaths/min, respiratory acidosis [pH < 7.3, arterial carbon dioxide tension > 50 mmHg], circulatory shock [vasopressor was needed to maintain mean arterial pressure > 65 mmHg] or disturbed consciousness level).

We recorded the patient's heart rate, mean arterial pressure, respiratory rate, and SpO_2 in room air at the time of admission to the emergency department. All other data, including ultrasound examination, were collected within 12 h of admission to the emergency room after stabilising the patient. The CT severity score was determined by an experienced radiologist who was blinded to clinical data. The CT score was calculated by dividing the lung into five anatomical zones: the left upper lobe, left lower lobe, right upper lobe, right middle lobe, and right lower lobe. Each lung lobe received a score of 0–5 according to the degree of lung affection, with a maximum score of 25 for both lungs [16].

Ultrasound examination of the diaphragm was performed by the same intensivist, who had more than 150 similar examinations, using a Samsung HS60 ultrasound machine (SAMSUNG MEDISON

CO., LTD. Seoul, Korea), with a 3–5 MHz curvilinear probe. In the semi-recumbent position, the transducer was placed over the lower intercostal space over the right anterior axillary line and then over the left mid axillary line for the right and left diaphragm assessments, respectively, at an angle of $\geq 70°$ in relation to the hemi-diaphragmatic domes. The patients were asked to perform their maximum inspiratory effort, and the caudal movement of the diaphragm toward the transducer during inspiration was recorded as an upward motion of the M-mode tracing. The diaphragmatic excursion was measured as the vertical distance from the baseline to the highest point of inspiration. The average of three successive measurements was calculated and used for data analysis. The intensivist who performed the ultrasound examination was not involved in recording the final outcomes of the study (ventilatory support–survival).

Outcomes

The primary outcome was the ability of the diaphragmatic excursion to predict the need for ventilatory support (defined as the need for non-invasive or invasive ventilation). Other outcomes included the ability of diaphragmatic excursion to predict patient mortality, the ability of other respiratory-related parameters, *i.e.*, respiratory rate in room air, SpO_2 in room air, and CT score at admission to predict the need for ventilatory support and patient mortality, demographic data (age, gender, body mass index, and comorbidity), Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE II) score, and laboratory data (ferritin, C-reactive protein, interleukin-6, D-dimer, and procalcitonin).

Sample size

The sample size was calculated using MedCalc Software version 14 (MedCalc Software bvba, Ostend, Belgium) to detect the area under the receiver operating characteristic curve (AUC) of 0.80 with a null hypothesis AUC curve of 0.5. Assuming that the incidence of ventilatory support in patients with severe COVID-19 is 35%, a minimum sample size of 38 patients (at least 13 patients needing ventilatory support) would achieve a study power and an alpha error of 90% and 0.05, respectively.

Statistical analysis

Continuous data were checked for normality using the Shapiro–Wilk test. Normally distributed data are presented as means (standard deviations) and skewed data are expressed as medians (quartiles). Comparisons between study groups (patients who required *versus* those who did not require ventilatory support and patients who survived *versus* those who died) were performed using the unpaired t-test or the Mann–Whitney test, as appropriate. Categorical variables were summarised as frequency (percentage) and analysed using the Chi-squared or Fisher's exact test, as appropriate. Receiver operating characteristic curves were constructed, and the AUC was calculated for diaphragmatic excursion, respiratory rate, SpO_2, and CT score. The best cut-off value was calculated using the Youden index, and the corresponding sensitivity, specificity, and positive and negative predictive values were then calculated. The AUCs were compared using the Hanley–McNeil test. The mean diaphragmatic excursion (calculated as the average of the right and left diaphragmatic excursion to allow their inclusion in the multivariable analysis), respiratory rate, SpO_2, and CT score as well as the age and gender were included in a multivariate logistic regression model to obtain the adjusted odds ratio and 95% confidence interval (CI). Firth's bias correction was used to deal with the separation issue in the logistic regression model for the need for ventilatory support. *P*-values of
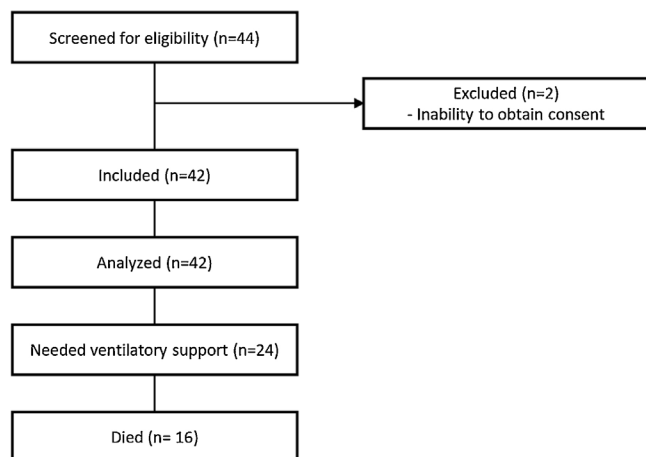
Fig. 1. Patients' enrolment and outcome.

less than 0.05 were considered statistically significant. Statistical analysis was performed using SAS OnDemand for academics (SAS Institute Inc., Cary, NC, USA), MedCalc Software version 14, and Statistical Package for Social Science (SPSS) software, version 26 for Microsoft Windows (Armonk, NY, IBM Corp.).

Results

Forty-four patients were screened for eligibility, and two patients were excluded due to an inability to obtain consent. Forty-two patients were included, and all patients were available for the final analysis (Fig. 1). The included patients had a median age (quartile) of 64 (55, 70) years, and 21 (50%) were males (Table 1). Twenty-four (57%) patients needed non-invasive ventilation, 19 (45%) required invasive mechanical ventilation, and 16 (38%) patients died. The number of patients who required vasopressor and renal replacement therapy during their stay in the ICU was 16

Table 1

Patient's characteristics and outcome data. Data are presented as mean (standard deviation), median (quartiles), and frequency (%).

Age (years)	64 (55, 70)
Male gender	21 (50%)
BMI (kg/m^2)	29 (5)
Comorbidity (%)	
Hypertension	23 (55%)
IHD	6 (14%)
Atrial fibrillation	2 (5%)
Stroke	2 (5%)
Diabetes mellitus	20 (48%)
CKD	5 (12%)
Hypothyroidism	3 (7%)
APACHE II score	12 (9, 16)
Onset of symptoms (days)	6 (3)
Heart rate (bpm)	94 (83, 100)
Mean arterial pressure (mmHg)	67 (62, 72)
SpO$_2$ at room air (%)	82 (72, 86)
RR (breath per minute)	34 (7)
Rt-DE (mm)	22 (13, 35)
Lt-DE (mm)	19 (10, 26)
M-DE (mm)	20 (12, 31)
CT score	12 (5)
Ferritin (pg/mL)	448 (225, 775)
C-reactive protein (mg/L)	95 (23, 143)
Procalcitonin (mcg/L)	0.20 (0.09, 0.50)
D-dimer (mcg/mL)	2.2 (1.2, 3.4)
Interleukin-6 (pg/mL)	99 (24, 205)

APACHE II: Acute Physiologic Assessment and Chronic Health Evaluation II, BMI: body mass index, CKD: chronic kidney disease, CT: computed tomography, IHD: ischaemic heart disease, Lt-DE: left diaphragmatic excursion, M-DE: mean diaphragmatic excursion, RR: respiratory rate, Rt-DE: right diaphragmatic excursion, SpO$_2$: peripheral oxygen saturation.
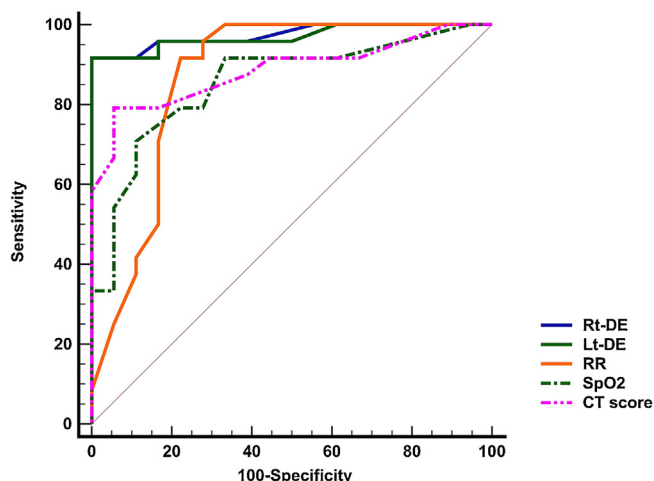

Fig. 2. AUC analysis for the ability of diaphragmatic excursion, RR, SpO$_2$, and CT score to predict patient's need for ventilatory support.
*Denotes significance in relation to the Rt-DE. AUC: area under receiver operating characteristic curve, CI: confidence interval, CT: computed tomography, Lt-DE: left diaphragmatic excursion, NPV: negative predictive value, PPV: positive predictive value, RR: respiratory rate, Rt-DE: right diaphragmatic excursion, SpO$_2$: peripheral oxygen saturation.

(38%) and 6 (14%), respectively. The median (quartiles) ICU stay was 8 (5, 11) days.

The AUCs (95% CI) for the ability of the right and left diaphragmatic excursion to predict the need for ventilatory support were 0.96 (0.85–1.00) and 0.94 (0.82–0.99), respectively (Fig. 2). The right diaphragmatic excursion showed a significantly higher AUC than SpO$_2$ ($P = 0.043$). Both right and left diaphragmatic excursion showed high sensitivity, specificity, and positive and negative predictive values in predicting the need for ventilatory support compared with the respiratory rate, SpO$_2$, and CT score (Fig. 2).

Furthermore, the right diaphragmatic excursion had the highest AUC to predict patient mortality in relation to the respiratory rate ($P = 0.003$), SpO$_2$ ($P = 0.040$), and CT score ($P = 0.046$) (Fig. 3).
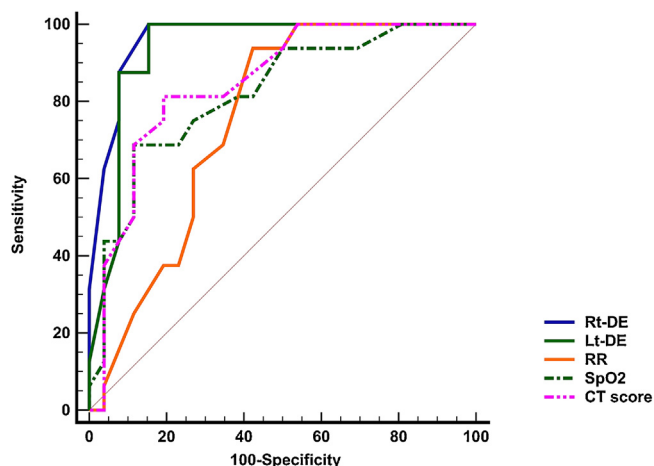
Fig. 3. AUC analysis for the ability of diaphragmatic excursion, RR, SpO$_2$, and CT score to predict patient mortality.
*Denotes significance in relation to the Rt-DE, † denotes significance in relation to the Lt-DE. AUC: area under receiver operating characteristic curve, CI: confidence interval, CT: computed tomography, Lt-DE: left diaphragmatic excursion, NPV: negative predictive value, PPV: positive predictive value, RR: respiratory rate, Rt-DE: right diaphragmatic excursion, SpO$_2$: peripheral oxygen saturation.

Table 2

Univariate for patient's need for ventilatory support and mortality.

	Need for ventilatory support		Mortality	
	Odd ratio (95% CI)	P value	Odd ratio (95% CI)	P value
Age	0.99 (0.95–1.04)	0.993	1.00 (0.96–1.05)	0.957
Male gender	0.46 (0.13–1.58)	0.215	0.28 (0.08–1.06)	0.062
BMI	0.99 (0.89–1.12)	0.956	1.02 (0.90–1.14)	0.811
APACHE II	1.17 (1.00–1.36)	0.044	1.12 (0.99–1.28)	0.080
Onset of symptoms (days)	1.18 (0.93–1.49)	0.167	1.23 (0.97–1.56)	0.095
Heart rate (bpm)[a]	1.10 (1.02–1.18)	0.011	1.03 (0.99–1.07)	0.187
MAP (mmHg)	0.93 (0.86–1.01)	0.090	0.98 (0.91–1.05)	0.549
Diabetes	0.57 (0.17–1.96)	0.374	0.33 (0.09–1.24)	0.101
Hypertension	0.64 (0.18–2.20)	0.475	1.10 (0.32–3.86)	0.879
IHD	1.60 (0.26–9.88)	0.613	0.79 (0.13–4.87)	0.796
Atrial fibrillation	0.74 (0.04–12.67)	0.835	1.67 (0.10–28.66)	0.725
Stroke	0.74 (0.04–12.67)	0.835	1.67 (0.10–28.66)	0.725
CKD	0.88 (0.13–5.87)	0.891	1.10 (0.16–7.38)	0.926
Hypothyroidism	1.55 (0.13–18.50)	0.731	3.57 (0.30–42.99)	0.316
SpO$_2$[a,b]	0.80 (0.70–0.93)	0.003	0.87 (0.79–0.95)	0.003
RR[a,b]	1.36 (1.14–1.63)	0.001	1.18 (1.04–1.33)	0.011
Rt-DE[a,b]	0.70 (0.56–0.88)	0.002	0.58 (0.35–0.94)	0.026
Lt-DE[a,b]	0.60 (0.42–0.85)	0.005	0.68 (0.54–0.86)	0.002
M-DE[a,b]	0.65 (0.49–0.86)	0.003	0.63 (0.43–0.91)	0.014
CT score[a,b]	1.52 (1.2–1.92)	0.001	1.36 (1.13–1.65)	0.001
Ferritin	1.002 (1.00–1.004)	0.051	1.00 (1.00–1.00)	0.173
C-reactive protein	1.00 (0.99–1.01)	0.179	0.99 (0.99–1.01)	0.794
Procalcitonin	1.91 (0.65–5.60)	0.237	1.98 (0.84–4.63)	0.117
D-dimer	1.12 (0.87–1.44)	0.386	0.95 (0.75–1.21)	0.695
Interleukin-6	1.00 (1.00–1.01)	0.067	1.00 (0.99–1.01)	0.133

APACHE II: Acute Physiologic Assessment and Chronic Health Evaluation II, BMI: body mass index, CKD: chronic kidney disease, CT: computed tomography, IHD: ischaemic heart disease, Lt-DE: left diaphragmatic excursion, MAP: mean arterial pressure, M-DE: mean diaphragmatic excursion, RR: respiratory rate, Rt-DE: right diaphragmatic excursion, SpO$_2$: peripheral oxygen saturation.

[a] Denotes significance for the need of ventilatory support.

[b] Denotes significance for mortality.

Table 3

Multivariable analysis for patient's need for ventilatory support and mortality.

	Need for ventilatory support		Mortality	
	Odd ratio (95% CI)	P value	Odd ratio (95% CI)	P value
Age	1.00 (0.93–1.08)	0.997	1.02 (0.91–1.13)	0.770
Male gender	0.89 (0.12–6.46)	0.998	0.43 (0.03–6.74)	0.550
SpO$_2$	0.98 (0.87–1.10)	0.994	0.91 (0.75–1.11)	0.365
Respiratory rate	1.05 (0.91–1.23)	0.997	0.83 (0.55–1.24)	0.358
M-DE[a]	0.88 (0.74–1.05)	0.995	0.55 (0.31–0.98)	0.042
CT score	1.05 (0.82–1.33)	0.994	0.94 ()	0.770

CT: computed tomography, M-DE: mean diaphragmatic excursion, SpO$_2$: peripheral oxygen saturation.

[a] Denotes significance for mortality.

Univariate analysis showed that diaphragmatic excursion, respiratory rate, SpO$_2$, and CT score were associated with an increased risk of the need for ventilatory support and mortality (Table 2). When including these factors in the multivariable analysis in addition to the age and gender, a low mean diaphragmatic excursion was the only independent predictor of patient mortality with an odds ratio (95% CI) of 0.55 (0.31–0.98), P-value 0.042 (Table 3).

Discussion

In patients with severe COVID-19, we showed that diaphragmatic excursion evaluated within 12 h of ICU admission has the highest ability to predict the need for ventilatory support as well as patient mortality compared to other respiratory measures (respiratory rate, SpO$_2$, and CT score). Furthermore, a low diaphragmatic excursion was an independent predictor of mortality regardless of patient's age or gender.

The diaphragm contributes to approximately 70% of the normal tidal volume during inspiration [6]. In patients with COVID-19, many mechanisms could contribute to diaphragmatic dysfunction, such as an uncontrolled immune response and increased risk of diaphragmatic muscle fibrosis [17]. Furthermore, there is evidence of direct viral infiltration of the diaphragm [16], whose severity might affect the extent of respiratory failure.

We found that a baseline SpO$_2$ < 79% in room air and a CT score > 12 can predict the need for mechanical ventilation with an excellent positive predictive value. Our results are consistent with the study by Mukhtar et al., who reported similar thresholds for SpO$_2$ and CT score to predict the need for ventilatory support in patients with COVID-19 [18]. Mahdjoub et al. also reported that a CT score of ≥ 13 can predict mechanical ventilation or death in patients with COVID-19 [19]. Our study evaluated diaphragmatic excursion upon admission in severe cases, in addition to the routinely assessed respiratory parameters. Few studies have reported the presence of COVID-19 associated diaphragmatic dysfunction, which was associated with failure of non-invasive ventilation as well as a failure to wean from invasive ventilation [11,12]. In this study, we aimed to provide new insights into the possible value of diaphragmatic evaluation in the selection of critical patients early after admission. Therefore, we evaluated the diaphragmatic excursion during the first 12 h of admission and found that it can predict serious outcomes more accurately than any other clinical or radiological variable. To the best of our knowledge, this is the first study to evaluate the value of diaphragmatic excursion as a tool for initial assessment in critically ill patients, specifically those with COVID-19. Diaphragmatic excursion is a simple measure that can be performed by junior staff who are commonly available during the pandemic. Diaphrag-

matic ultrasound is faster than CT and more economic compared to laboratory investigations because one machine can be used for many patients without consumables or blood sampling. We suggest that diaphragmatic excursion can be used as a triaging tool, especially when there is a high load of patients; patients with severe COVID-19 and poor diaphragmatic excursion should be prioritised for admission to higher specialised units, while those with good diaphragmatic excursion would be mostly treated with simple oxygen therapy and are unlikely to receive ventilatory support. Early detection of severe cases would improve the early selection of patients who might benefit from referral to centres with extracorporeal membrane oxygenation services. Survival among extracorporeal membrane oxygenation-assisted patients was improved in centres with a high extracorporeal membrane oxygenation case volume [20]. However, it is noteworthy that a very high diaphragmatic excursion on one side could signify the presence of paralysis on the contralateral side [21]. This study has some limitations. It was performed in a single centre. We did not evaluate other diaphragmatic parameters, such as thickening fraction, because we aimed to use the simplest measures (*e.g.*, diaphragmatic excursion), which can be performed without extensive training. We did not record the duration of steroid therapy before hospital admission; however, all patients received steroid therapy during their care according to the institutional protocol. We did not include patients with mild hypoxaemia because these patients were not admitted to our hospital. We were unable to blind the treating physicians to the results of CT imaging because it was a basic component of routine patient care; however, the radiologist was blinded to the clinical status of the patient while calculating the CT score, and the attending intensivists were blinded to the results of the diaphragmatic examination. Finally, all ultrasound examinations were performed by a single sonographer; therefore, further studies are warranted to confirm our cut-off values and evaluate the benefit of integrating diaphragmatic excursion in patient management.

In conclusion, diaphragmatic excursion, evaluated within 12 h after admission, can accurately predict the need for ventilatory support and mortality in patients with severe COVID-19. The low diaphragmatic excursion was an independent risk factor for in-hospital mortality. A right diaphragmatic excursion < 24 mm can predict the need for ventilatory support with a positive predictive value of 100%, and a right diaphragmatic excursion < 18 mm can predict mortality with a positive predictive value of 80%.

Human and animal rights

The authors declare that the work described has been carried out in accordance with the Declaration of Helsinki of the World Medical Association revised in 2013 for experiments involving humans as well as in accordance with the EU Directive 2010/63/EU for animal experiments.

Informed consent and patient details

The authors declare that this report does not contain any personal information that could lead to the identification of the patient(s).

The authors declare that they obtained a written informed consent from the patients and/or volunteers included in the article. The authors also confirm that the personal details of the patients and/or volunteers have been removed.

Disclosure of interest

Dr. Ahmed Hasanin is an editor at the *Anaesthesia Critical Care & Pain Medicine* journal. The authors declare that they have no conflict of interest with this work.

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Author contributions

All authors attest that they meet the current International Committee of Medical Journal Editors (ICMJE) criteria for authorship.

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