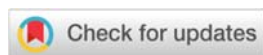


ORIGINAL ARTICLE

Diaphragmatic Thickening Fraction as a Predictor of Early Treatment Failure in Acute Exacerbation of COPDRIMSHA ALI SHEAIKH¹, HINA AWAN², MUNTAQA BUTT³, AKHTAR ALI⁴, NOOR E SEHER⁵, HAMZA AKRAM⁶, MUHAMMAD KASHIF⁷¹Registrar Anesthesia Ghurki Hospital, Lahore²Medicine Speciality Registrar Shalamar institute of health sciences. **Email:** dr.hinaawan1234@gmail.com³Medicine Speciality Registrar Shalamar institute of health sciences. **Email:** dr.hinaawan1234@gmail.com⁴Assistant Professor, Pulmonology, Shalamar Institute of Health Sciences. **Email:** drakhtarshah@gmail.com⁵Department of Biological Science, Keele University, Keele, Staffordshire ST5 5BG, United Kingdom. **Email:** nooreseher7989@gmail.com⁶Master in Management Department, Business School Hertfordshire University, Hatfield, AL10 9AB, United Kingdom. **Email:** chhamzajalal0300@gmail.com⁷Master of Science in Management University of Hertfordshire Hatfield, AL10 9AB, United Kingdom. **Email:** Muhammadkashif02183@gmail.com**Correspondence to:** Rimsha Ali Sheaiikh, **Email:** rimshale97@gmail.com**This Editorial may be cited as:**

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**ABSTRACT**

Background: If acute exacerbation of chronic obstructive pulmonary disease is not prevented, it can develop into hypercapnic respiratory failure and noninvasive ventilation failure. Bedside ultrasonography of diaphragm thickening fraction could be used as an early predictor of respiratory muscle dysfunction.

Objective: To determine whether diaphragmatic thickening fraction predicts early treatment failure in patients with acute exacerbation of chronic obstructive pulmonary disease receiving noninvasive ventilation.

Methods: This was a prospective observational cohort study of 200 adults who were admitted in Jinnah Hospital Lahore from March 2024 to March 2026. Diaphragm thickness was measured at end-expiration and peak inspiration at baseline and two hours after starting noninvasive ventilation. The thickness of the diaphragm was measured and the average difference between the inspiratory and expiratory thickness was expressed as a percent of the inspiratory thickness, as the diaphragmatic thickening fraction. Failure of treatment was defined as endotracheal intubation or death in less than 72 hours.

Results: Early treatment failure occurred in 52 patients (26.0%). The baseline diaphragmatic thickening fraction was lower in the patients who failed treatment, as compared to those who were successfully treated ($18.5 \pm 6.3\%$ vs $28.2 \pm 7.6\%$, $p < 0.001$). The difference was greater after two hours ($17.9 \pm 6.2\%$ versus $32.4 \pm 7.5\%$; $p < 0.001$). A two hour threshold of $\leq 23\%$ detected failure with sensitivity of 86.5%, specificity of 82.4% and area under the curve of 0.91. Diaphragmatic thickening fraction $\leq 23\%$ was the best independent predictor of failure (adjusted odds ratio 9.72; 95% confidence interval 4.16–22.71; $p < 0.001$) after adjustment. It has a high negative predictive value, potentially helping to identify those patients who are likely to continue to receive noninvasive ventilation successfully.

Conclusion: The 2-hour diaphragmatic thickening fraction was an independent predictor of early treatment failure and might help guide timely escalation of respiratory care.

Keywords: acute exacerbation of COPD; diaphragmatic thickening fraction; diaphragm ultrasonography; noninvasive ventilation; respiratory failure; treatment failure

INTRODUCTION

COPD is a progressive lung disease that involves a persistent reduction in lung function, chronic lung symptoms and frequent exacerbations (clinical worsening) of the disease¹. Commonly, acute exacerbations of chronic obstructive pulmonary disease manifest by an increase in sputum purulence, quantity, and dyspnoea. Episodes can be severe and can result in acute hypercapnic respiratory failure especially in patients with advanced disease, limited respiratory reserve, or multiple co-morbid conditions. These exacerbations are an important cause of short-term mortality, prolonged recovery, hospitalization and emergency attendance².

Noninvasive ventilation (NIV) has been a common first ventilatory approach in patients who are appropriate and in whom acute exacerbation of chronic obstructive pulmonary disease (COPD) has led to respiratory acidosis³. It will decrease work of breathing, increase ventilation of alveoli, remove carbon dioxide and may prevent need for invasive mechanical ventilation. However, some patients do not respond to adequate medical treatment and ventilatory support. If this deterioration is not appreciated early enough, this could delay intubation, exacerbate respiratory distress and put the patient at risk of poor clinical outcomes⁴.

Response to treatment is typically evaluated by respiratory rate, level of consciousness, use of accessory muscles, measurement of arterial blood gases, oxygenation, hemodynamic stability, and tolerance of ventilatory interface⁵. These parameters are clinically useful, but do not directly reflect the performance of respiratory muscles. Arterial pH and carbon dioxide can also only be affected in the presence of a large degree of physiologic compromise. This simple bedside tool assessing respiratory muscle function could therefore be used to better identify patients at risk of failure of treatment at an early stage⁶.

Diaphragm is the most important muscle for inspiration and is the central muscle in effective ventilation⁷. Airway obstruction and dynamic hyperinflation in an acute exacerbation flattens and shortens the diaphragm, thereby affecting the mechanics of the diaphragm. These changes at the same time lead to increased work of breathing, as airway resistance increases and intrinsic PEEP (IPEEP) increases. If the diaphragm can no longer produce enough exertion to meet this increased demand, respiratory muscle fatigue, an increase in carbon dioxide retention, and ventilatory failure can ensue⁸.

Bedside ultrasonography is a practical and noninvasive means of assessing diaphragmatic structure and function⁹. Thickness of the diaphragm can be measured when it is exhaling and inhaling in the zone of

apposition. Diaphragmatic thickening fraction is the percent increase in muscle thickness that occurs during inspiration, and is used as a measure of diaphragmatic contraction. A low thickening fraction may be due to poor recruitment, decreased contractile capacity, or respiratory muscle fatigue. Repeated use of technique is possible, no radiation exposure to patient, and may be used in emergency / critical-care situations¹⁰.

Diaphragmatic dysfunction has been suggested to correlate with poor response to noninvasive ventilation (NIV) previously¹¹. The best time to measure and most appropriate predictive threshold is still unclear, however. One measurement taken on the day of admission can be influenced by a lot of distress, irregular breathing and starting ventilator settings. A re-assessment after a brief treatment period may give a better idea of whether the performance of the diaphragm is improving. Persistent low thickening with ventilatory support may thus help identify those patients with insufficient respiratory muscle reserve and the likelihood of intubation or early death¹².

The aim of the present study was to assess the predictive power of the DTF for early treatment failure in patients with AEC of COPD receiving NIV¹³. It was also designed to see if there were differences between baseline and early follow-up measurements and to determine if there was any additional value of diaphragmatic thickening fraction beyond common clinical and arterial blood gas parameters¹⁴.

MATERIALS AND METHODS

Study Design and Setting: This is a two-year prospective observational cohort study (March 2024–March 2026) in the Department of Pulmonology and Respiratory Critical Care, Jinnah Hospital Lahore. To determine the usefulness of diaphragmatic thickening fraction in predicting early treatment failure in patients hospitalised with acute exacerbation of chronic obstructive pulmonary disease. To reduce selection bias, all eligible patients were sequentially entered.

Study Population: Two hundred adult patients admitted for acute exacerbation of chronic obstructive pulmonary disease (COPD) who required the use of noninvasive ventilation were included. COPD was defined by a history of the disease, or by previous spirometric verification of persistent airflow limitation, or by review of medical records. Acute exacerbation was defined as a deterioration in dyspnoea, cough, sputum volume or purulence that occurred outside of the normal day-to-day fluctuation in these symptoms and necessitated additional therapy.

Inclusion Criteria: The inclusion criteria were patients 40 years old or older with a confirmed diagnosis of chronic obstructive pulmonary disease (COPD) who presented with an acute exacerbation of COPD (AECOPD) with hypercapnic respiratory failure. Patients were selected if, after initial controlled oxygen, standard medical management, arterial blood gas analysis revealed a partial pressure of carbon dioxide > 45 mmHg and an arterial pH between 7.20 and 7.35. Patients were only included if they were deemed to be fit for initial testing of NIV.

Exclusion Criteria: Patients that required immediate endotracheal intubation at presentation, respiratory or cardiac arrest, severe hemodynamic instability, inability to protect the airway, massive aspiration, uncontrolled vomiting, facial trauma or anatomic abnormality that would prevent proper mask placement were excluded. Other exclusion criteria were diaphragmatic paralysis, any neuromuscular disease, recent thoracic or upper abdominal surgery, pneumothorax, major chest-wall deformity, interstitial lung disease, primary cardiogenic pulmonary oedema, active pulmonary tuberculosis and poor diaphragm visualization on ultrasound. Patients with a documented Do Not Intubate (DNI) order were also excluded as treatment limitation could impact the primary outcome.

Sampling Technique and Sample Size: Non-probability (consecutive) sampling technique was used. In the study period all eligible patients were approached until the required sample size of 200 patients was obtained. Consecutive recruitment was chosen to guarantee that the study population was representative of the typical population of patients with acute exacerbation of chronic obstructive pulmonary disease admitted to hospital.

Initial Clinical Assessment: Demographic and clinical data was collected at the time of enrolment by the use of a structured data collection form. Documented variables were: age, sex, BMI, smoking status, time since diagnosis of COPD, past hospitalizations, past NIV use, home oxygen use, major comorbidities, maintenance inhaler therapy and baseline disease severity (available in a subset with spirometry). The precipitating factor that was presumed, such as respiratory infection, poor treatment adherence, environmental exposure, or unknown precipitating factors, was also documented.

At admission, a detailed clinical examination was done. Documentation of respiratory rate, heart rate, blood pressure, body temperature, saturation of oxygen, level of consciousness, use of accessory muscles, and presence of paradoxical abdominal movement. Arterial blood gas analysis before or at start of noninvasive ventilation was

collected, and included arterial pH, partial pressure of arterial oxygen, partial pressure of arterial carbon dioxide, and bicarbonate concentration and lactate level. Laboratory tests were carried out according to the clinical protocol: complete blood count, serum electrolytes, renal and liver function tests, C-reactive protein, chest radiography and electrocardiography.

Standard Medical Treatment: Standard therapy for AEC of COPD was provided to all patients. Controlled oxygen therapy was provided to keep oxygen saturations between 88% and 92%. Short acting beta-2 agonists and anticholinergic bronchodilator were administered at regular intervals by nebulisation. Systemic corticosteroids were given, if not contraindicated and antibiotic therapy was started if bacterial infection was clinically suspected. Fluid management, electrolyte correction, secretion clearance, thromboprophylaxis and associated medical conditions were provided as per individual clinical need.

Noninvasive Ventilation Protocol: Noninvasive ventilation was administered via a properly fitted oronasal mask with a bilevel positive airway pressure device or intensive-care ventilator in pressure-support mode. Initial inspiratory PAP was typically 10-14 cmH₂O and expiratory PAP was 4-6 cmH₂O. The inspiratory pressure was slowly titrated based on respiratory rate, tidal volume, patient comfort, mask leak, ABG parameters and clinical response. Supplemental oxygen was given to achieve the desired oxygen saturation. Mask fit, patient-ventilator synchrony, pressure discomfort and airway secretions were assessed and corrected on a regular basis if needed.

Clinical response was evaluated after 1 and 2 hours of noninvasive ventilation and at regular intervals thereafter. Arterial blood gas was repeated two hours after treatment was started or sooner if the condition worsened. The choice of continuation of noninvasive ventilation, ventilator setting change, or endotracheal intubation was at the discretion of the attending clinical team and was independent of the research measurements.

Diaphragmatic Ultrasonography: A portable ultrasound machine with high frequency linear transducer was used for the ultrasonography of the diaphragm. The patients were examined in semi-recumbent position. The right hemidiaphragm was chosen for evaluation as the liver was a consistent acoustic window and the zone of apposition was more visible. Transducer was placed perpendicular to the chest wall between the 8th and 10th intercostal space close to the anterior or mid-axillary line.

Diaphragm was found to be a three layered structure with two hyperechoic layers (pleural and peritoneal) and a relatively hypoechoic muscular layer. Measurement of the

thickness of the diaphragm was taken from the centre of the pleural line to the centre of the peritoneal line. Three successive respiratory cycles with measurements taken at end-expiration and at peak inspiration. Three technically acceptable measurements were taken and the average of the three was used for the analysis.

Diaphragmatic Thickening Fraction Measured:

Diaphragmatic thickening fraction was estimated by the difference between the end-inspiratory and end-expiratory diaphragm thickness divided by end-expiratory diaphragm thickness and expressed as a percentage. The measurement was given as percentage. A higher value in the range reflected a greater inspiratory diaphragmatic thickening and a lower value reflected a decreased diaphragmatic contraction.

Ultrasound assessment was carried out at the start of noninvasive ventilation post initial stabilisation and 2 hours after the start of treatment. When possible, clinically, the ventilator setting remained the same throughout each ultrasound examination. The examiner who performed ultrasonography was blinded to the clinical outcome and was not involved in the decision to intubate.

The Reliability of Ultrasound measurements: A randomly chosen subset of patients was examined independently by a second trained examiner blinded to the first examiner's measurements to determine the reliability of the measurements. Intraclass correlation coefficient (ICC) was used to assess intraobserver and interobserver agreements. The operators underwent supervised training and practice examination prior to the start of the study to ensure uniformity in the placement of the transducers and the acquisition and measurement of images.

Definition of Early Treatment Failure: The primary outcome was early treatment failure defined as failure within 72 hours of start of noninvasive ventilation. Failure of treatment was taken as the need for endotracheal intubation or death in this period. Endotracheal intubation was taken into account when patients were becoming more and more acidotic, respiratory distress was present or worsening, severe hypoxia despite optimizing respiratory support, inability to protect the airway, decreased level of consciousness, excessive respiratory secretions, hemodynamic instability, respiratory arrest, or intolerance of noninvasive ventilation despite corrective measures.

Treatment success was defined as clinical improvement and correction or stabilization of respiratory acidosis, respiratory rate, accessory muscle use, mental status, and noninvasive ventilation without intubation or death within 72 hours.

Secondary Outcomes: Secondary endpoints were in-hospital mortality, time to noninvasive ventilation (NIV) weaning, intensive-care admission, time to intubation (in those who required it), intensive-care length of stay, total hospital length of stay, and correlation between serial changes in DTF and clinical response. The two-hour and baseline DTF were also compared with the respiratory rate, arterial pH, partial pressure of arterial carbon dioxide, and oxygenation parameters.

Data Collection Procedure: All clinical, laboratory, ventilatory, ultrasonographic and outcome data was entered in a proforma designed for the study. Confidentiality was maintained by providing each participant with a different study code. Completed forms were checked periodically for completeness and consistency of information. Data was then entered into an electronic database, double checked independently, and subjected to statistical analysis.

Statistical Analysis: IBM SPSS Statistics version 29.0 software was used for statistical analysis. Graphic and Shapiro–Wilk tests were used to evaluate the normality of continuous variables. Normally distributed variables were reported as mean and standard deviation and non-normally distributed variables were reported as median and interquartile range. Frequencies and percentages were used to present categorical variables.

Patients were split into treatment-success and treatment-failure groups. Independent-samples t test or Mann–Whitney U test was used to compare continuous variables, as appropriate. Chi square test or Fisher exact test were used to compare categorical variables. Paired statistical tests were used to assess changes in diaphragmatic thickening fraction from baseline to the 2 hour assessment.

Baseline DTF and 2h-DTF were used to predict, and receiver operating characteristic curve analysis was performed. This area under the curve and the corresponding 95% confidence interval was calculated. The optimal cut-off value was chosen by the Youden index. Sensitivity, specificity, PPV, NPV and overall diagnostic accuracy were calculated for the chosen cut-off point.

Variables that were clinically important and that had a univariable p-value < 0.10 were selected for the multivariable logistic regression. A parsimonious model was used to evaluate if the thickening fraction of the diaphragm was an independent predictor of failure of early treatment after accounting for potential confounding factors including previous use of noninvasive ventilation, age, respiratory rate, arterial pH, partial pressure of arterial carbon dioxide, and oxygenation. Adjusted odds ratios (with 95% confidence intervals) were provided. The

presence of multicollinearity and calibration of the model were evaluated prior to interpretation. Two-sided p-values < 0.05 were regarded as significant.

Ethical Considerations: The study was started after approval by Institutional Review Board/ Ethical Review Committee. Each patient or, if at the time of consent the patient was temporarily unable to give because of the respiratory difficulty, a legally authorized representative gave written informed consent. There was no interference with normal clinical practice and all clinical decisions were left to the attending physicians. The privacy of patients was respected and only used for research.

RESULTS

Patient Enrollment and Early Treatment Outcomes: A total of 224 consecutive patients with acute exacerbation of chronic obstructive pulmonary disease admitted from March 2024 to March 2026 were screened for participation. Ten patients needed urgent endotracheal intubation, five patients had severe hemodynamic instability, four patients had known neuromuscular and/or diaphragmatic conditions, three patients had poor ultrasonographic visualization of the diaphragm and two patients refused to participate. Thus, 200 patients with both baseline and two-hour diaphragm ultrasound were included in the final study population.

The number of early treatment failures were 52 patients (26.0%). Of these, 47 patients needed invasive ventilation within 72 hours of initiating NiV, and five patients died with a rapid cardiorespiratory deterioration and failed to receive invasive ventilation. The remaining 148 patients did well with noninvasive ventilation and standard medical management, and were considered a treatment success.

Demographic and clinical characteristics at baseline.

The average age of the subjects was 67.8 ± 8.8 years. There were 126 male and 74 female patients in the study population. No significant differences were found between the treatment-success and treatment-failure groups in terms of age, sex, BMI, current smoking status, IHD, DM, and MAP.

Advanced chronic obstructive pulmonary disease (COPD), history of previous admission for noninvasive ventilation (NIV) and long term home oxygen therapy (LTHOT) were more likely to be features of patients who had early treatment failure. Of those with treatment failure 80.8% had severe or very severe airflow limitation compared with 64.2% of those treated successfully.

Treatment-failure group was significantly different with regard to respiratory rate and heart rate at presentation. These patients also had a more severe

respiratory acidosis (as indicated by a lower mean arterial pH and higher partial pressure of arterial carbon dioxide). Median C-reactive protein concentration was significantly higher and oxygenation was poorer in the treatment-failure group. Table 1 shows the baseline demographic, clinical and laboratory features.

Diaphragmatic Ultrasound Findings: The two groups did not have a significant difference in baseline end-expiratory diaphragm thickness. By contrast, patients who went on to have treatment failure had significantly thin end-inspiratory diaphragm measurements at baseline. The mean baseline diaphragmatic thickening fraction was $18.5 \pm 6.3\%$ in the treatment-failure group compared with $28.2 \pm 7.6\%$ in the treatment-success group.

This diaphragmatic function difference was accentuated after 2 hours of noninvasive ventilation. Patients who successfully achieved treatment showed a mean increase in diaphragmatic thickening fraction from 28.2% to 32.4% at baseline and 2 hours, respectively. No such increase was found in the patients with treatment failure (baseline 18.5%, 2 hours 17.9%).

A mean increase of 4.2 ± 4.6 percentage points was seen in the treatment-success group, and a mean decrease of 0.6 ± 4.1 percentage points was seen in the treatment-failure group. This respiratory rate to diaphragm thickening fraction ratio also was significantly higher in patients with treatment failure. The results are shown in Table 2.

The reproducibility of diaphragm ultrasound measurements was assessed in 40 randomly selected patients. The intraclass correlation coefficient for the repeated measurements obtained by the same operator was 0.93 (95% confidence interval: 0.88 to 0.96). There was also strong agreement between the two trained operators with an intraclass correlation coefficient of 0.89 and a 95% confidence interval of 0.82 to 0.94.

PP of Diaphragmatic Thickening Fraction: Both the baseline and the 2-hour diaphragmatic thickening fraction were found to be a predictor of early treatment failure, as demonstrated by receiver operating characteristic analysis. Baseline diaphragmatic thickening fraction had an area under the curve of 0.84 (95% confidence interval, 0.78–0.90). The baseline value of 21% or less was determined to have a 76.9% sensitivity and 79.7% specificity.

The two-hour diaphragmatic thickening fraction had the best one by one predictive value with an AUC of 0.91, CI (0.87-0.95). The best cut-off score was determined to be 23% or less. This threshold obtained an accuracy of 83.5%, sensitivity of 86.5%, specificity of 82.4%, positive predictive value of 63.4% and negative predictive value of 94.6%.

The predictive power of the 2 hour diaphragmatic thickening fraction was higher than that of arterial pH,

respiratory rate, partial pressure of arterial carbon dioxide, oxygenation ratio and change in diaphragmatic thickening fraction. Comparative results are given in Table 3.

Clinical Outcomes According to the Two-Hour Diaphragmatic Thickening Fraction: 23% of patients (n = 71) had a two hour diaphragmatic thickening fraction $\leq$ 23%, and 129 patients had a two hour diaphragmatic thickening fraction $>$ 23%. 71 patients had low DTF, of which 45 (63.4%) had an early treatment failure. In contrast, only 7 of 129 patients had a value $>$ 23% and failed treatment.

59.2% of patients with a thickening fraction of diaphragm of 23% or below required intubation within 72 hours, while 3.9% of those with a value above 23% required intubation within 72 hours. Intensive-care admission rate and in-hospital mortality rate were also significantly higher for the low-thickening group.

Patients with decreased diaphragmatic thickening had longer intensive care unit and total hospital lengths of stay. The low-thickening group also had a higher 30-day readmission rate among survivors of hospital discharge. The clinical outcomes for the two-hour cut-off are given in Table 4.

Multivariable Predictors of Early Treatment Failure:

Severe chronic obstructive pulmonary disease, previous admission for noninvasive ventilation, long-term home oxygen therapy, elevated respiratory rate, arterial pH below 7.25, elevated arterial carbon dioxide, impaired oxygenation, and 2-hour diaphragmatic thickening fraction of 23% or less were associated with early treatment failure in univariable analysis.

Adjustment for clinically relevant variables showed that a diaphragmatic thickening fraction of 23% or less was the most powerful independent predictor of treatment failure. Low 2-hour diaphragmatic thickening fraction were associated with almost tenfold adjusted odds for treatment failure.

A respiratory rate of $\geq$ 30 breaths/min and a pH of $<$ 7.25 were also independently associated with treatment failure. Admission with previous noninvasive ventilation had borderline significance, but age and an arterial oxygen pressure to inspired oxygen fraction ratio $<$ 200 were not independently significant. Table 5 presents the results for multivariable regression.

Table 1: Baseline demographic, clinical, and laboratory characteristics according to early treatment outcome

Variable	Overall population (n=200)	Treatment success (n=148)	Treatment failure (n=52)	p-value
Age, years	67.8 $\pm$ 8.8	67.1 $\pm$ 8.5	69.7 $\pm$ 9.3	0.063
Male sex, n (%)	126 (63.0)	91 (61.5)	35 (67.3)	0.455
Female sex, n (%)	74 (37.0)	57 (38.5)	17 (32.7)	0.455
Body mass index, kg/m ²	23.6 $\pm$ 4.1	23.8 $\pm$ 4.0	23.2 $\pm$ 4.3	0.365
Current smoker, n (%)	72 (36.0)	50 (33.8)	22 (42.3)	0.271
Global Initiative for Chronic Obstructive Lung Disease stage III or IV, n (%)	137 (68.5)	95 (64.2)	42 (80.8)	0.027
Previous admission requiring noninvasive ventilation, n (%)	67 (33.5)	41 (27.7)	26 (50.0)	0.003
Long-term home oxygen therapy, n (%)	59 (29.5)	37 (25.0)	22 (42.3)	0.019
Ischemic heart disease, n (%)	49 (24.5)	35 (23.6)	14 (26.9)	0.636
Diabetes mellitus, n (%)	61 (30.5)	43 (29.1)	18 (34.6)	0.454
Respiratory rate, breaths per minute	28.6 $\pm$ 5.6	26.9 $\pm$ 4.5	33.4 $\pm$ 5.4	$<$ 0.001
Heart rate, beats per minute	104.8 $\pm$ 17.1	101.1 $\pm$ 14.9	115.4 $\pm$ 18.2	$<$ 0.001
Mean arterial pressure, mmHg	88.7 $\pm$ 13.5	89.6 $\pm$ 12.8	86.2 $\pm$ 15.1	0.116
Arterial pH	7.28 $\pm$ 0.07	7.30 $\pm$ 0.06	7.22 $\pm$ 0.07	$<$ 0.001
Partial pressure of arterial carbon dioxide, mmHg	72.9 $\pm$ 15.8	68.8 $\pm$ 13.1	84.6 $\pm$ 16.7	$<$ 0.001
Arterial oxygen pressure to inspired oxygen fraction ratio	218 $\pm$ 64	230 $\pm$ 59	183 $\pm$ 65	$<$ 0.001
Serum bicarbonate, mmol/L	31.4 $\pm$ 5.7	31.2 $\pm$ 5.5	32.0 $\pm$ 6.2	0.382
C-reactive protein, mg/L	47 (24–82)	42 (21–72)	66 (34–101)	0.006

Table 2: Diaphragmatic ultrasound measurements according to early treatment outcome

Ultrasound measurement	Overall population (n=200)	Treatment success (n=148)	Treatment failure (n=52)	p-value
Baseline end-expiratory diaphragm thickness, mm	1.87 $\pm$ 0.35	1.89 $\pm$ 0.34	1.81 $\pm$ 0.38	0.158
Baseline end-inspiratory diaphragm thickness, mm	2.34 $\pm$ 0.43	2.42 $\pm$ 0.40	2.11 $\pm$ 0.42	$<$ 0.001
Baseline diaphragmatic thickening fraction, %	25.7 $\pm$ 8.3	28.2 $\pm$ 7.6	18.5 $\pm$ 6.3	$<$ 0.001
Two-hour end-expiratory diaphragm thickness, mm	1.86 $\pm$ 0.34	1.88 $\pm$ 0.33	1.80 $\pm$ 0.37	0.145
Two-hour end-inspiratory diaphragm thickness, mm	2.39 $\pm$ 0.44	2.49 $\pm$ 0.39	2.12 $\pm$ 0.42	$<$ 0.001
Two-hour diaphragmatic thickening fraction, %	28.6 $\pm$ 9.6	32.4 $\pm$ 7.5	17.9 $\pm$ 6.2	$<$ 0.001
Change in diaphragmatic thickening fraction, percentage points	3.0 $\pm$ 5.2	4.2 $\pm$ 4.6	-0.6 $\pm$ 4.1	$<$ 0.001
Two-hour respiratory rate-to-diaphragmatic thickening fraction ratio	1.11 $\pm$ 0.68	0.83 $\pm$ 0.31	1.91 $\pm$ 0.77	$<$ 0.001

Table 3: Receiver operating characteristic analysis for prediction of early treatment failure

Predictor	Optimal cutoff	Area under the curve	95% confidence interval	Sensitivity, %	Specificity, %
Baseline diaphragmatic thickening fraction	≤21%	0.84	0.78–0.90	76.9	79.7
Two-hour diaphragmatic thickening fraction	≤23%	0.91	0.87–0.95	86.5	82.4
Change in diaphragmatic thickening fraction	≤1.5 percentage points	0.81	0.74–0.87	73.1	78.4
Respiratory rate	≥30 breaths per minute	0.82	0.76–0.88	78.8	73.0
Arterial pH	<7.25	0.80	0.73–0.86	71.2	80.4
Partial pressure of arterial carbon dioxide	≥78 mmHg	0.76	0.69–0.83	67.3	75.7
Arterial oxygen pressure to inspired oxygen fraction ratio	<200	0.72	0.64–0.79	65.4	70.9

Table 4: Clinical outcomes according to the two-hour diaphragmatic thickening fraction threshold

Outcome	Diaphragmatic thickening fraction ≤23% (n=71)	Diaphragmatic thickening fraction >23% (n=129)	p-value
Early treatment failure, n (%)	45 (63.4)	7 (5.4)	<0.001
Endotracheal intubation within 72 hours, n (%)	42 (59.2)	5 (3.9)	<0.001
Death before intubation within 72 hours, n (%)	3 (4.2)	2 (1.6)	0.355
Intensive-care admission, n (%)	45 (63.4)	24 (18.6)	<0.001
In-hospital mortality, n (%)	12 (16.9)	4 (3.1)	<0.001
Total hospital stay, days	11 (8–15)	7 (5–10)	<0.001
Intensive-care stay among admitted patients, days	7.2 ± 3.6	4.1 ± 2.4	<0.001
Thirty-day readmission among patients discharged alive, n (%)	13 of 59 (22.0)	13 of 125 (10.4)	0.035

Table 5: Multivariable logistic regression analysis of predictors of early treatment failure

Predictor	Adjusted odds ratio	95% confidence interval	p-value
Two-hour diaphragmatic thickening fraction ≤23%	9.72	4.16–22.71	<0.001
Arterial pH <7.25	3.48	1.53–7.91	0.003
Respiratory rate ≥30 breaths per minute	2.84	1.23–6.56	0.014
Previous admission requiring noninvasive ventilation	2.11	0.97–4.58	0.059
Arterial oxygen pressure to inspired oxygen fraction ratio <200	1.98	0.88–4.46	0.098
Age per one-year increase	1.02	0.98–1.07	0.268

Final multivariable model showed good discrimination with an area under the receiver operating characteristic (ROC) curve of 0.93. The two-hour diaphragmatic thickening fraction was added to the model that contained only age, respiratory rate, arterial pH, previous noninvasive ventilation, and oxygenation, yielding better performance.

Principal Findings: Early treatment failure occurred in approximately one-quarter of patients with acute exacerbation of chronic obstructive pulmonary disease receiving noninvasive ventilation. Diaphragmatic thickening fraction did not increase after 2 hours of ventilatory support and was lower at baseline in patients who failed treatment. Two-hour diaphragmatic thickening fraction of 23% or less was the most discriminating fraction in isolation and was independently associated with treatment failure, even when conventional clinical and arterial blood gas parameters were included in the analysis. Its high negative predictive value for a value >23% meant that a low likelihood of intubation or early death was associated with a value >23%.

DISCUSSION

The present study provided solid evidence for the strong association of diaphragmatic thickening fraction to early treatment failure in acute exacerbation of chronic obstructive pulmonary disease patients evaluated by noninvasive ventilation¹. The baseline and 2-hour ventilatory support DTFs were significantly lower in patients requiring endotracheal intubation and those who died within 72 hours. A diaphragmatic thickening fraction of 23% or less on the two-hour measurement proved to be the best predictor of patients at significantly higher risk of treatment failure².

About a quarter of the study population experienced early treatment failure³. This ratio relates to the severity of the clinical state of the patients enrolled, who all suffered from acute hypercapnic respiratory failure and required NIV. The failure group had higher respiratory rate, more aggravated respiratory acidosis, higher arterial carbon dioxide level, more pronounced tachycardia and lower percentage of oxygen saturation. These data show higher ventilatory demand/respiratory reserve mismatch at admission⁴.

Diaphragmatic dysfunction can help to directly cause this imbalance⁵. In an acute exacerbation the diaphragm is flattened and shortened due to worsening of the airflow obstruction and dynamic hyperinflation. This poor arrangement decreases the efficiency of diaphragmatic contraction, and increases inspiratory effort necessary to begin the flow of air due to intrinsic positive end-expiratory pressure. If there is a continued need for breathing, the diaphragm can get tired and stop working effectively. Thus, reduced thickness of the diaphragm is a physiologically plausible measure of restricted respiratory-muscle capacity⁶.

It is also important that there was no difference in end-expiratory diaphragm thickness between the treatment groups⁷. There was no clear difference between the diaphragm thickness of the patients who responded to treatment and those who did not. Inspiratory thickness and diaphragm thickening fraction, however, were significantly different between the groups. The results indicate that during acute respiratory failure, more clinically relevant information is obtained from dynamic diaphragmatic contraction than from anatomical thickness alone⁸.

The diaphragmatic thickening fraction at 2 hours was more effective than the baseline measurement⁹. For those who successfully responded to the noninvasive ventilation, there was an obvious increase in diaphragmatic thickening after the first two hours of ventilation. This rise could be attributed to a decrease in inspiratory loading, improvement in diaphragm geometry, increase in alveolar ventilation and effective unloading of the respiratory muscles. No clinically significant differences were found in patients with treatment failure, who had a slight decrease in DTF¹⁰.

This is an observation that supports serial diaphragm assessment and not isolated¹¹. Baseline measurement is affected by severity of respiratory distress, patient effort, ventilator synchrony and the amount of hyperinflation present at admission. After a period of noninvasive ventilation, reassessment might be more useful at showing if the diaphragm is responding to therapy. If thickening is not observed despite ventilatory support, this suggests that there is continued muscle dysfunction and inadequate physiological recovery¹².

The 23% two-hour diaphragmatic thickening fraction cutoff had a high sensitivity and specificity for early treatment failure¹³. It had a high negative predictive value which was clinically relevant. Patients whose values were above this threshold had a low risk of intubation and mortality within the first 72 hours. This discovery indicates that preserved diaphragmatic contraction could be used to identify patients who are likely to respond well to ongoing use of noninvasive ventilation¹⁴.

PPV was lower than NPV, meaning that a decrease in diaphragmatic thickening alone is not a good predictor of intubation¹⁵. Low values do not always mean that the patient will not recover, as optimal noninvasive ventilation and medical treatment can still help the patient recover. Trends in arterial blood gas, level of consciousness, respiratory distress, oxygenation, hemodynamic stability, protection of the airway, amount of secretions, and tolerance should still be used to determine escalation of respiratory support¹⁶.

The ratio of respiratory rate to the thickness of the diaphragm was also higher significantly in the treatment-failure group¹⁷. This ratio is a combination of the respiratory demand and the diaphragmatic contractile activity. A patient with rapid breathing, who lacks diaphragmatic thickening, will probably have a poor load:capacity ratio. This variable was not chosen as a primary predictive marker, but could be useful for other physiological data and would be worth exploring¹⁸.

Two hour diaphragmatic thickening fraction of 23% or less was the most significant independent predictor of treatment failure as confirmed by multivariable analysis¹⁹. It was also an important association after adjusting for other factors such as previous noninvasive ventilation, respiratory rate, arterial pH, and oxygenation. This finding demonstrates the value of diaphragm ultrasonography to provide prognostic information that is additional to the clinical and arterial blood gas parameters that are routinely assessed²⁰.

Independent predictors of failure were also: arterial pH < 7.25 and respiratory rate ≥ 30 breaths per minute⁴. Severe acidosis is indicative of poor alveolar ventilation and the latter stage of the respiratory physiology disturbance. If there is continued tachypnoea, it means there is ongoing respiratory distress and high ventilatory workload. These traditional indices together with reduction of diaphragmatic thickening may be more complete measure of response to treatment than any one of them¹¹.

Those who had a low two-hour diaphragmatic thickening fraction had higher rates of intensive-care admission, endotracheal intubation, in-hospital mortality and 30-day readmission⁷. They had longer intensive-care and total hospital stays. These associations indicate that impaired diaphragmatic function is not only associated with immediate failure of noninvasive ventilation, but it also may be a marker for more overall disease severity and lower physiological reserve¹⁶.

In an acute care environment, there are a number of practical benefits of diaphragmatic ultrasound². It is non-invasive, repeatable, portable and does not use ionizing radiation. Measurements at the bedside are available without interrupting respiratory support or the need to transport an unstable patient. In the present study, the

intraobserver and interobserver reliability were high, indicating the possibility of reproducible measurements when operators are trained in a standardized way¹⁴.

However, diaphragm ultrasonography should be cautiously undertaken and analyzed⁶. The measurement may be influenced by the position of the probe, the patient's position, the respiratory pattern, the settings of the ventilator with pressure support, leakage of the mask, and patient-ventilator interaction. The use of diaphragmatic thickening fraction in routine treatment protocols therefore requires standardization of the acquisition technique¹⁸.

There are limitations to the study⁹. It was performed at one centre only, and the results may not be applicable to other centres or populations of patients. Just the right hemidiaphragm was studied as it offers a more dependable acoustic window. It was not possible to fully exclude the effect of pressure-support levels on inspiratory thickening. There were no physiological measurements available for comparison such as transdiaphragmatic pressure or EMG of the diaphragm¹³.

The cut-off point of 23% was used based on the current study population and might not be generally applicable without external validation⁵. Other factors that could have affected diaphragmatic performance include baseline nutritional status, chronic hyperinflation, frailty, long-term exposure to steroids, and pre-existing respiratory-muscle weakness. While important clinical confounders were entered into the regression model, unknown factors may have influenced the observed associations¹⁷.

However, the prospective design, consecutive enrolment, serial ultrasound measurements, clearly defined outcome and blinded ultrasound assessment add to the strength of findings³. The study suggests that early serial echocardiographic assessment of the diaphragm in patients with AECOPD who are being treated with noninvasive ventilation may be useful in addition to clinical assessment and arterial blood gases^{19,20}.

CONCLUSION

The strength of association between reduced diaphragmatic thickening fraction and early treatment failure in those with acute exacerbation of chronic obstructive pulmonary disease treated with noninvasive ventilation was strong. The measurement taken after two hours of treatment was more accurate in predicting intubation or early death than the initial measurement and was independently associated with intubation/early death after controlling for standard clinical factors. A diaphragmatic thickening fraction of 23% or less for two hours was indicative of a significant risk of adverse

outcomes, while a higher fraction was associated with a high chance of successful treatment. A bedside tool for identifying those patients who need closer observation, re-assessment of the arterial blood gas, optimisation of ventilatory support and timely consideration of invasive ventilation may therefore be useful serial diaphragm ultrasonography. Diaphragmatic thickening fraction should NOT be a substitute for clinical judgement and accepted indications for intubation. Its primary use is as an adjunct to routine assessment for direct information about respiratory-muscle function. However, larger multi-centre studies are needed to validate the proposed cut-off and to explore the role of diaphragm ultrasonography in the standardisation of decision-making pathways.

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