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Ultrasound-guided diaphragm evaluation and outcomes in severe acute exacerbation of chronic obstructive pulmonary disease (uDISCO Study): an observational study

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Abstract

Acute exacerbations of chronic obstructive pulmonary disease (COPD) are associated with compromised diaphragmatic function. This can be evaluated using point-of-care ultrasound. The association of diaphragm function with hospital length of stay or mortality has not been assessed earlier. This study aimed to evaluate the correlation of diaphragmatic function with length of hospital stay, mortality, and non-invasive ventilation (NIV) failure in severe acute exacerbation of COPD. Diaphragmatic excursion and thickening index (Tdi) were evaluated with ultrasound-guided assessment in individuals with severe acute exacerbation of COPD at the time of hospitalization. The individuals were evaluated for length of stay in survivors, NIV ventilation failure in those requiring NIV therapy, and mortality in non-survivors. A total of 110 individuals were screened, and 60 of these were enrolled. A total of 55 individuals survived, and 5 died. The length of stay had a negative correlation with excursion (R: -0.78, $p<0.001$) and Tdi (R: -0.96, $p<0.001$). The excursion and Tdi were smaller by 30% and 50%, respectively, in the event of NIV failure compared to NIV success. Excursion 1.96 cm [area under receiver-operating characteristic curve (AUROC): 0.958] or Tdi 92% (AUROC: 0.974) were associated with length of stay 8 days. Excursion 1.48 cm (AUROC: 0.75) or Tdi 51.2% (AUROC: 0.8) were associated with NIV failure. Tdi 40% was associated with a high risk of mortality (RR: 22.67, $p=0.035$). Smaller diaphragmatic excursion, or Tdi, correlated with prolonged LoS, mortality, and NIV failure.

Key words: excursion, diaphragmatic thickening fraction index, diaphragm dysfunction, transdiaphragmatic pressure, sonography, NIV failure.

Introduction

Chronic obstructive pulmonary disease (COPD) is a heterogeneous disorder characterized by chronic inflammation of airways and/or destruction of airspaces [1,2]. It is associated with impairment of respiratory muscles [1]. The motion and function of the diaphragm are compromised in stable COPD due to static hyperinflation leading to restriction of craniocaudal movement [3-5]. The diaphragm partly adapts to this over a period of time. During exacerbations, however, due to dynamic hyperinflation there is an exaggerated caudal displacement of the diaphragm and as a result, myofiber shortening [6,7]. Further, acute cellular injury, cytokine release, and myofibroblast activation also independently decrease the diaphragm's contractility [8-14]. This compromises the ability to generate transdiaphragmatic pressure and leads to ventilatory compromise [3,15].

Diaphragmatic function can be accurately measured using transdiaphragmatic pressure measurement [15]. This is an invasive method and requires insertion of a balloon-transducer catheter into the esophagus and stomach [15]. Diaphragm function can also be measured non-invasively, using ultrasonography (US) [15,16]. Diaphragmatic excursion is the distance by which the diaphragm moves between end-expiration and end-inspiration. Diaphragmatic thickening index (Tdi) or thickening fraction is the percentage by which the diaphragm thickens over its end-expiratory thickness.

In stable COPD, diaphragmatic excursion correlates with the severity of illness [17-20]. In critically ill COPD requiring invasive mechanical ventilation (IMV), US based diaphragm measurements can predict weaning and extubation failures [21-25]. During an acute exacerbation of COPD (AECOPD), US-based diaphragm evaluation can moderately predict the risk of non-invasive ventilation (NIV) failure [26-29]. However, the correlation of Tdi or excursion with length of stay (LoS) in severe COPD is largely unknown.

A Medline search was conducted using Medical Subject Headings: ((((ultrasound) OR (sonography)) AND (copd)) AND (acute exacerbation)) AND (diaphragm)). The search returned a total of 23 results which were then accessed and reviewed for content. Out of 23 studies, there were five original research articles which studied diaphragmatic excursion, inspiratory or expiratory thicknesses, or Tdi using US in acute exacerbation of COPD. Among these five studies, four had evaluated the role of diaphragmatic ultrasound parameters in predicting the success or failure of non-invasive ventilation (NIV) [26-29]. The fifth study compared Tdi and excursion between an acute exacerbation and stable COPD [30]. None of these studies assessed US-based diaphragmatic evaluation in the context of LoS in AECOPD. The European Respiratory Society

has identified areas in thoracic ultrasound where knowledge is lacking and stated that its role in AECOPD needs more research [31]. The objective of the present study was to assess the correlation of impaired diaphragm function, assessed by US, with outcomes in AECOPD requiring hospitalization.

Materials and Methods

The study was conducted at an academic research institute; between June 2021 and May 2022. Approval was obtained from the institutional ethics board before commencing the research (IEC/2012-PGIMSR/1658). Voluntary and informed consent was procured from each participant before enrolment in the study. The sample size calculated for the study was sixty individuals.

The diagnosis of COPD and acute exacerbation were made according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2021 guidelines [1]. Co-existing bronchial asthma, posttuberculosis pulmonary disease, diffuse parenchymal lung disease, neuro-muscular disorders, pleural effusion or thickening, kyphoscoliosis, malignancy with mediastinal involvement, ascites or peritonitis, liver or splenic abscess, previous thoracic surgery, or post-abdominal surgery were identified as a-priori exclusion criteria. Study participants were treated and managed by pulmonologists not involved with data recording or analysis.

Assessment for diaphragmatic function

Evaluation of diaphragm function by US was performed at the time of hospitalization using the MySono U6 Diagnostic ultrasound system (Samsung Medison, Seoul, South Korea) in B-mode connected to linear (5-12 MHz) and curvilinear (2-5 MHz) probes. The standard and universally accepted technique for diaphragmatic sonography was applied in the study [16,32]. The patient was semi-reclined at a 45 degrees angle to the horizontal. To assess the zone of apposition, the linear probe was placed in the 8-10th intercostal spaces between the mid- and posterior-axillary lines. If diaphragm was not identified till the 10th space, the probe was placed further lower, in the 10-12th spaces. The identification of the diaphragm was based on its three layered appearance on B-mode, a non-echogenic layer surrounded on each side by relatively thinner echogenic layers of peritoneum and pleura. Then, using the M-mode, a measurement was taken each at end-inspiration and end-expiration. Tdi was calculated from these values as 100x([end-inspiration thickness]–[end-expiration thickness])/(end expiration thickness). Diaphragmatic excursion was assessed using the curvilinear probe placed in the subcostal area between the midclavicular and anterior axillary lines. The probe was directed superiorly, medially, and posteriorly. The excursion

was calculated as the distance by which the diaphragm moved between end-inspiration and end-expiration. Each measurement was taken three times, and the mean values were selected for analysis.

Definitions

1. Length-of-stay (LoS): The duration (days) from hospitalization to discharge. A LoS 8 days was taken a priori as prolonged stay.
2. Days-to-death (DtD): The duration (days) from hospitalization to death.
3. NIV success: Patients who were treated with NIV during their stay with successful avoidance of IMV. This group represents the successful prevention of endotracheal intubation and IMV by the use of NIV.
4. NIV failure: Patients who were treated with NIV during their stay but required IMV because of respiratory worsening despite NIV.
5. Lower limit of normal (LLN) for Tdi: The LLN for Tdi was used during the post-hoc analysis. This has been previously established (Tdi<40%) by Boussuges and colleagues [33].

Statistical analyses

Participant details, parameters, and outcomes were recorded in an online excel sheet. Level-of-significance (alpha) was stipulated as 0.05. Continuous variables expressed as mean/standard deviation and median/first- and third-quartiles. Shapiro-Wilk test was used to check for normality of data. Percentages of categorical variables or frequency were analysed using the chi-square. Scatter plots were formulated for trend assessment of diaphragmatic parameters in relation to LoS or DtD. Correlation was evaluated for excursion, Tdi, and LoS among each other and with other parameters. Pearson and Spearman correlation analyses were used for normal and nonnormal data. Regression analysis was then performed to establish significantly correlating parameters. Receiver-operating characteristic (ROC) curve was used for evaluating the ability of Tdi and excursion to identify a LoS 8 days and NIV failure.

Results

A total of 110 individuals were screened and assessed for enrolment. Sixty individuals qualified and consented for enrolment (Figure 1). The demographic and clinical parameters are presented in *Supplementary Table 1*.

Outcome of hospitalization: survived vs died

Among a total of 60 individuals, five (8.33%) died and 55 (91.67%) survived. The mean age was 59.4 (±6.73) and 65.16 (±8.68) years, respectively (p=0.16). The median ages were 57 (Q1-Q3: 55-66) and 67 (Q1-Q3: 59-71) years, respectively. The mean body mass index (BMI) was 18.91 (±2.45) and 20.04 (±3.95) kg/m^2, respectively (p=0.53). The two groups were comparable for age, BMI, duration of smoking, pack years of smoking, cause of exacerbation, previous need of IMV or NIV, and incidence of respiratory acidosis (*Supplementary Table 1*).

The mean diaphragmatic excursion was 1.59 (±0.53) cm in individuals who survived and 0.62 (±0.5) cm in those who died. The difference was statistically significant (p=0.003, 95% Confidence Interval, 95%CI: -1.6612 to -0.3688, difference relative to survivors:(-61%)). The mean inspiratory diaphragmatic thickness was significantly smaller among those who died (0.20 (±0.10) cm) compared to those who survived (0.49 (±0.24) cm), (p=0.011, relative difference:(-59.18%)). The mean expiratory diaphragmatic thickness was 0.16 (±0.09) cm and 0.26 (±0.12) cm among the two groups, respectively (p=0.06, relative difference:(-38.46%)). The mean Tdi was significantly smaller in those who died compared to those who survived (29.51 ±8.87% vs 90.57 ±49.1%, p=0.008, relative difference:(-67.42%)).

Diaphragm function in survivors

Among survivors, Tdi had a weak but significant negative correlation with the number of previous exacerbations and respiratory rate (*Supplementary Table 2*). Diaphragmatic excursion had a moderate and significant negative correlation with the number of previous exacerbations. Excursion and Tdi had a strong and significant positive correlation between each other. However, neither Tdi nor excursion significantly correlated with age, height, pack-years of smoking, duration of illness, duration of exacerbation, or blood gas parameters (*Supplementary Table 2*).

The scatter plots of LoS versus US parameters are presented in Figure 2. The LoS was found to have a strong and significant negative correlation with Tdi (R:(-0.96), p:<0.001). The LoS also had a strong and significant negative correlation with diaphragmatic excursion (R:(-0.78), p:<0.001). However, it did not bear a significant correlation with age, BMI, pack-years of smoking, duration of illness, duration of exacerbation, number of exacerbations, respiratory rate, or blood gas parameters (*Supplementary Table 3*). Multilinear regression analysis indicated a very strong collective significant effect between Tdi, excursion, and LoS, (F=58.85, p<0.001, R^2=0.69, R^2_{adj}=0.68). Further evaluation of the individual predictors indicated that Tdi (t=(-3.881), p<0.001)

and excursion (t=(-2.253), p=0.028) were significant predictors in the model (LoS= 21.15 - $0.064xTdi_{(\%)}$ - $2.615xExcursion_{(cm)}$).

Out of 55 survivors, 38 (69.09%) had a LoS 8 days. A Tdi 92% was associated with a LoS 8 days (AUROC:0.974, sensitivity:89.47%, specificity:100%, accuracy:92.73%). Excursion 1.96 cm was also associated with a LoS 8 days (AUROC:0.958, sensitivity:97.37%, specificity:82.35%, accuracy:92.73%). The ROC analysis of Tdi and excursion are presented in *Supplementary Table 4* and Figure 3.

Diaphragm function in nonsurvivors

Scatter plots of the measured values of diaphragm-functional parameters and the number of DtD in nonsurvivors are presented in Figure 2. Diaphragmatic excursion had a weak and non-significant negative correlation with DtD (R:(-0.1), p-value:0.75) (*Supplementary Table 5*). There was a strong but non-significant positive correlation of Tdi with DtD (R:0.7, p-value:0.28, covariance:1.75). Using ROC analysis, an excursion 0.7 cm (AUROC:0.905, sensitivity:80%, specificity:90.91%, accuracy:90%) or Tdi 40% (AUROC:0.947, sensitivity:100%, specificity:89.29%, accuracy:90%) were associated with mortality.

NIV failure

Out of a total of 60 participants, 41 received NIV. Failure of NIV was observed in five (12.2%). Excursion was smaller in the NIV failure group (1.1 ±0.44 cm, relative difference:(-29.49%)) compared to the NIV success group (1.56 ±0.55 cm, p=0.08) (*Supplementary Table 6*). The Tdi was significantly smaller when NIV failed compared to when it succeeded (44.21 ±18.75% vs 88.81 ±46.60%, p=0.04, relative difference:(-50.22%)). Using ROC analysis, a Tdi 51.2% (AUROC:0.8, sensitivity:80%, specificity:75%, accuracy:75.61%) or excursion 1.48 cm (AUROC:0.75, sensitivity:100%, specificity:58.33%, accuracy:63.41%) were associated with NIV failure (*Supplementary Table 4* and Figure 3).

Tdi<LLN

A post-hoc analysis was performed with Tdi<LLN (<40%). Out of 60 participants, 51 had normal Tdi (40%) and nine had impaired Tdi (<40%). One (2%) out of 51 individuals with Tdi 40% and four (44.44%) out of nine individuals with Tdi<40% died (*Supplementary Table 7*). Mortality was significantly greater with impaired compared to normal Tdi (RR:22.67, p=0.035, Chi-square:4.43, 95%CI: 2.85 to 180.28). Further, five out of nine individuals with Tdi<40%, required NIV. Two

out of these five (40%) suffered from NIV failure. Out of 51 individuals with Tdi 40%, 35 required NIV. Three out of these 35 (8.67%) suffered from NIV failure. The difference was statistically significant (p=0.048). The risk of NIV failure was greater with Tdi<40% compared to Tdi 40% (RR: 4.67, 95%CI: 1.02 to 21.43).

Discussion

This study assessed diaphragmatic function by excursion and Tdi in sixty individuals hospitalized with AECOPD. It evaluated these parameters between survivors and non-survivors, and their relationship with LoS. To the best of our knowledge, this is the first study that evaluated the association of Tdi and excursion with a prolonged LoS. It also assessed the association of Tdi and excursion with NIV failure.

In the current study, age, BMI, smoking exposure, prior history of NIV or IMV, and incidence of respiratory acidosis were comparable between survivors and non-survivors. Among survivors in this study, Tdi and excursion correlated negatively with the number of previous exacerbations. A correlation between reduced diaphragm function and recurrent exacerbations is well established [3,6,9].

Age, BMI, pack-years, duration of COPD, number of previous exacerbations, and blood gases are important parameters for the management of COPD. However, the present study did not find a significant correlation between LoS and any of these parameters. The only parameters that were significantly associated with prolonged LoS were Tdi and diaphragmatic excursion. LoS showed a significant and strong negative correlation with Tdi and a significant and moderate negative correlation with excursion. The current study found that Tdi 92% or excursion 1.41 cm could identify a LoS 8 days with high sensitivity (Tdi:89.47%, excursion:97.37%) and high accuracy (Tdi:92.73%, excursion:92.73%). Greater the compromise of diaphragmatic function, the longer the time to its recovery and the LoS were. This is likely due to myofiber shortening caused by dynamic hyperinflation in AECOPD [34]. As a result, the ability to generate higher transdiaphragmatic pressure and consequently, ventilation are also compromised [34]. Further, the acute cellular injury, cytokine release, and myofibroblast activation also independently lead to a reduced diaphragm function [8-15].

In the current study, Tdi and excursion were smaller by 50% and 30%, respectively, in NIV failure compared to NIV success. It also found that Tdi 51.2% or excursion 1.48 cm were sensitive (Tdi:80%, excursion:100%) and accurate markers for NIV failure. Previously, a Tdi<20% has been found to be associated with NIV failure in AECOPD. Antenora and colleagues evaluated the

association of low Tdi with NIV failure, length of ICU stay, or mortality in 41 individuals with AECOPD [32]. The ICU mortality was significantly greater in individuals with a Tdi<20% (40%) compared to Tdi 20% (12.9%, p=0.04) [27]. Marchioni and colleagues found a greater mortality with Tdi<20% (40%) compared to Tdi 20% (16%, p=0.03) [26]. It is worth noting that a Tdi<20% is a validated cut-off to identify severe diaphragmatic dysfunction such as what is present in critically ill neuromuscular disease, myopathy, or neuropathy [35,36]. However, an AECOPD is an acute worsening of diaphragmatic function. Using a low cut-off of 20% fails to identify mild or moderate impairment. Further, individuals with severe diaphragmatic dysfunction (Tdi<20%), are likely to be suffering severe critical or chronic illness(es) with a high risk of NIV failure or mortality even for non-respiratory causes [35,36]. Using the LLN, therefore, is more pragmatic in real world scenarios where all severity levels of impairment are encountered in AECOPD at the time of hospitalization. In an observational study, Boussuges and colleagues established the LLN for Tdi at 40% [33]. In the post-hoc analysis of the current study, a Tdi <40% was also found to be associated with a greater risk of mortality (RR:22.67). Further, Tdi<40% also had a significantly greater risk of NIV failure (RR: 4.67).

Potential applications of the findings of this study are in identifying individuals at high risk of NIV failure, prolonged LoS, or mortality using Tdi or excursion. These parameters reliably correlate with transdiaphragmatic pressures with the advantage of non-invasiveness of US [35,36]. Measurement of transdiaphragmatic pressure by balloon-transducer catheters can also predict NIV failure, however, the invasiveness poses challenges in a severely dyspneic or agitated patient [15]. It may also lead to unnecessary delays in treatment initiation. The US can be performed at the bedside during routine assessment of acutely worsened dyspnea in COPD, while evaluating for differential diagnoses like pneumothorax, heart failure, pneumonia, pulmonary embolism, or pleural effusion [2,37].

The present study is not free from limitations. A larger sample size might have enabled the assessment of a larger group of non-survivors and of NIV failures. The approved study period was twelve months, five of which were marred by the COVID-19 pandemic. Secondly, assessment at follow-up visits may have revealed data about recovery or persistence of diaphragmatic impairment beyond hospital stay and the risk for future exacerbations. Thirdly, the study population had a significantly skewed sex distribution, with 96.67% (n=58) males and 3.33% (n=2) females.

The strength of this study lies in finding correlating parameters for adverse outcomes without requiring patient data before the time of hospitalization. Assessment by US is a recommended

tool for differential diagnoses in AECOPD with little potential for harm. It was the first study that evaluated the correlation of Tdi and excursion with LoS. Another strength lies in using the LLN (40%) for Tdi. Studies till date have used the 20% cut-off, which identifies severe diaphragmatic dysfunction in chronic critically ill patients. In the real world scenario, non-severe impairment can also be diagnosed using the LLN. Lastly, the study design was such that US evaluation did not impact the hospitalization decision or management of the patients in any way.

Conclusions

This observational study evaluated diaphragm function and outcomes in severe AECOPD. There was a significant negative correlation of Tdi and excursion with LoS. Smaller Tdi and excursion were associated with mortality, prolonged LoS(8 days) , and NIV failure. A Tdi<90% or excursion<1.9 cm were associated with a prolonged LoS and Tdi<50% or excursion<1.5 cm were associated with NIV failure. Further, Tdi<LLN (40%) carried a high risk of mortality. Larger scale studies could provide more insights into these correlations.

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Online supplementary material:
Supplementary Table 1. Clinical and demographic details of study participants (n=60).
Supplementary Table 2. Correlation analysis for diaphragm function and individual parameters
Supplementary Table 3. Correlation analysis of length of hospital stay and individual parameters
Supplementary Table 4. Receiver-operating analysis and performance of thickening index and excursion for outcomes: length of stay and NIV failure.
Supplementary Table 5. Correlation analysis for days to death in nonsurvivors.
Supplementary Table 6. Comparison of diaphragm parameters in individuals in whom NIV succeeded *vs*. failed.
Supplementary Table 7. Comparison for individuals with Tdi <40% and 40%.

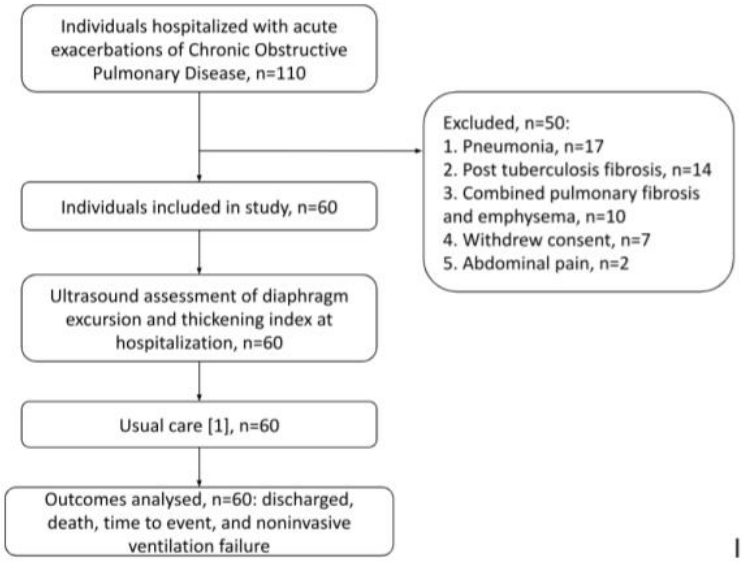

Figure 1. Study flow for the research.

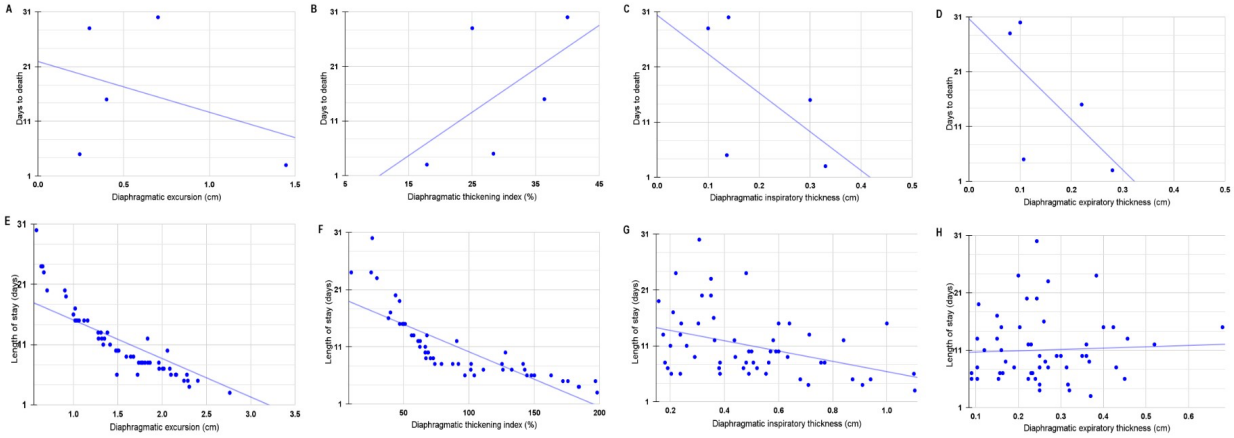

Figure 2. Scatter plots and trend lines for diaphragmatic parameters and days to outcome. Days to death in nonsurvivors (panels A-D): Diaphragmatic excursion (A), diaphragmatic thickening index (B), inspiratory (C) and expiratory (D) thicknesses. Length of stay in survivors (panels E-H): Diaphragmatic excursion (E), diaphragmatic thickening index (F), inspiratory (G) and expiratory (H) thicknesses.

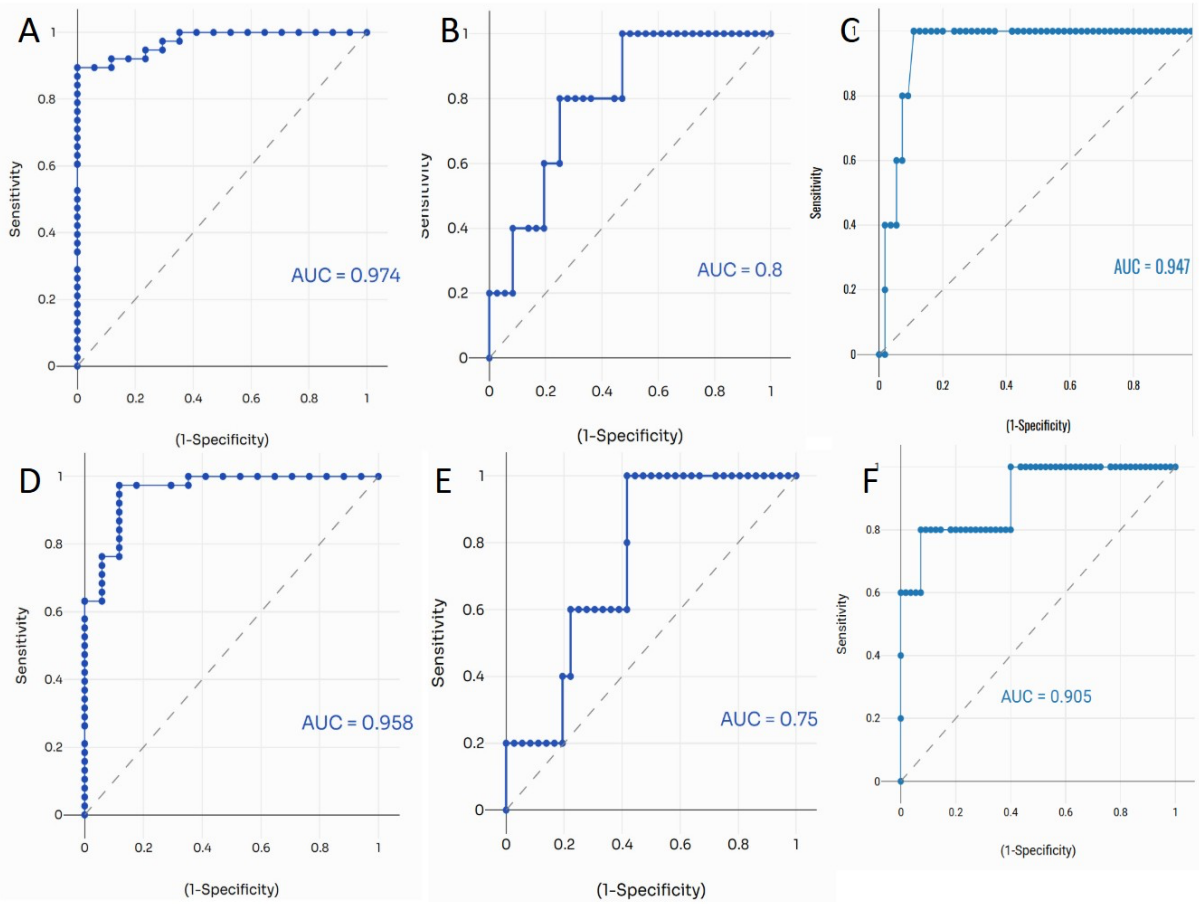

Figure 3. Receiver-Operating Characteristic curves. Panels A-D: Diaphragmatic thickening index for identifying LoS 8 days (A), NIV failure (B), and death (C). Panels D-F: Diaphragmatic excursion for identifying LoS 8 days (D), NIV failure (E), and death (F). LoS: Length of stay, NIV: Non-invasive ventilation.