Diaphragmatic Function Assessed by Bed Side Ultrasonography in Patients with Sepsis or Septic Shock Admitted to Intensive Care Unit

Amal Zaki[1]*, Helmy Hassan El Ghawaby[1], Mostafa Mahmoud Mohammed Gad[2], Amira Mohamed Ismail[1], Amr Shafiq Nawar[1]

[1]Department of Critical Care, Cairo University, Kasr Alainy Hospital, Cairo, Egypt; [2]Department of Radiology, Cairo University, Kasr Alainy Hospital, Cairo University, Cairo, Egypt

Abstract

BACKGROUND: Sepsis and septic shock are major problems faced the healthcare systems all over the world every year. The ultrasound (US) is a simple, non-invasive, easily accessible technique, and showed great accuracy in diaphragm assessment.

AIM: We evaluated the diaphragmatic function assessed by US in patients with sepsis and septic shock and correlated these assessments with different parameters.

MATERIALS AND METHODS: A prospective observational study carried out on 30 patients admitted to the intensive care unit (ICU) diagnosed with sepsis and/or septic shock. Both diaphragmatic excursion (DE) and thickness fraction (diaphragm thickening fraction [TDI] %) were assessed by US on admission and every 48 h along the patients' ICU stay.

RESULTS: In the current study, there was a statistically significant reverse relationship between mortality and the different diaphragmatic function parameters (DE on admission, average DE, on admission TDI%, average TDI%). On the other hand, the DE (on admission and average) showed a statistically significant reverse relation with the need and duration of mechanical ventilation (MV) while the TDI% showed a statistically significant reverse relation only with the duration of MV. Besides, there was a statistically significant direct relationship between successful weaning from MV and all the measured parameters.

CONCLUSION: We proposed that the diaphragmatic function parameters (DE on admission, average DE, on admission TDI% and average TDI%) assessed by US of septic ICU patients could be used as a predictor of the need, duration, and successful weaning from MV and also as a predictor of mortality.

Introduction

The improper host response to infection could lead to a serious condition of organs failure known as sepsis. Clinically, sepsis could be identified as a progressive increase in the sequential (Sepsis-related) Organ Failure Assessment score >2 and it is accompanied by an increase in the in-hospital mortality >10% [1]. The septic shock is the worst scenario of host response characterized by significant circulatory, cellular, and metabolic dysfunctions and associated with a higher mortality rate more than sepsis alone. Clinically, the septic shock is recognized by a requirement of vasopressor to keep the mean arterial pressure >65 mm Hg and serum lactate level >2 mmol/L (>18 mg/dL) in the absence of decreased plasma volume [1]. Unsurprisingly, the occurrence of sepsis and septic shock together upsurge the in-hospital mortality rate >40%.

Nowadays, a great interest in the diaphragmatic functions has grown steadily concerning its adverse clinical effect on weaning outcomes, the duration of mechanical ventilation (MV) [2], survival, and long-term consequence in the intensive care unit (ICU) patients [3], [4]. The deployment of ultrasound (US) to assess ICU patients is strongly recommended [5] due to its portability, safety, rapidity, and easily obtained results. Concerning the assessment of the diaphragmatic functions, the US could provide many helpful data about both the structural and functional components of the diaphragm at the bedside [6], [7]. In addition, the US accuracy for diaphragm assessment seems to be the same as most other imaging techniques [8], [9], [10], [11], [12].

The diaphragmatic excursion (DE) and the diaphragm thickening fraction (TDI%) are two sonographic parameters measured to predict the diaphragmatic functions. The DE measures the distance that the diaphragm can move during the respiratory cycle while the TDI% [13] reflects variation in the thickness of the diaphragm during the respiratory effort and is calculated as (thickness at end-inspiration–thickness at the end-expiration)/ thickness at the end of the expiration percentage; which normally >20% [13].

Materials and Methods

Study population

From June 2019 to January 2020, they study was conducted on 30 consecutive patients above 18 years admitted to the ICU diagnosed with sepsis or septic shock on admission and through their ICU stay.

Patient management

Examination and diagnosis

On admission, all the patients in the study were subjected to the following:

- Full history taking
- Complete clinical examination (conscious level recorded by the Glasgow Coma Scale, hemodynamics (HR, BP, temp, RR, UOP, SPO2), acute physiology and chronic health evaluation II score (APACHE II), complete neurological, chest, cardiac, and abdominal examination)
- Full laboratory investigation (arterial blood gases, random blood sugar, renal function test (urea and creatinine), cardiac enzymes, coagulation profile, complete blood count, blood lactate quantitative C-reactive protein (CRP), cultures and sensitivity for detecting the source of sepsis and causative organism)
- Imaging study (chest X-ray, ECG, Transthoracic ECHO, and diaphragmatic US to assess the diaphragmatic functions [DE and TDI%]).

Treatment

Meticulous management of all patients according to Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock [14], [15].

Assessment of the diaphragmatic function: Using commercially available Samsung Medison SonoAce R3 portable US. Both excursion (with M mode using Medison CN Convex (2–8 MHz) abdominal, OB/Gyn, renal transducer), and diaphragmatic thickness fraction (with B mode using Medison Linear [5–12 MHz] 60 mm Small Parts, Breast, Vascular) were measured on admission and every 48 h along the patients' ICU stay as follows:

The DE

- Was assessed with M-mode US device at the bedside with a low-frequency curvilinear or phased-array transducer (2–8 MHz) using the probe will be placed lower intercostal or subcostal between the mid-clavicular and anterior axillary lines on the right side, so that the US beam reached perpendicularly the posterior third of the right hemi diaphragm and on the left side of the diaphragm was studied from a lower intercostal or subcostal approach
- The diaphragm inspiratory amplitude (excursion) was measured from the M-mode sonography. The first caliper was placed at the foot of the inspiration slope on the diaphragm echoic line, and the second caliper was placed at the apex of this slope. For measurements, the amplitude of excursion was measured on the vertical axis of the tracing from the baseline to the point of the maximum height of inspiration on the graph. Several respiratory cycles were recorded, and measurements were average from three different cycles. Abnormal mobility was considered if <1.2 cm in the supine position [13].

The TDI%

- Thickness assessment of the diaphragm could be obtained at the zone of apposition on an intercostal view using two-dimensional B-mode US and requires a high-frequency linear-array probe (5–12 MHz). The transducer was positioned at the mid-axillary line at the intercostal space between the seventh and eighth ribs or the eighth and ninth ribs to obtain an ultrasonographic image in the sagittal plane. So that the US beam reached perpendicularly the posterior third of the hemi diaphragm in the supine position with an average inclination of 45 degree
- The diaphragm was identified as a three-layer structure consisting of one relatively non-echogenic muscle layer coated in two echogenic lines determined by peritoneal serosa and diaphragmatic pleura. Diaphragmatic thickness was measured at the end-inspiration and -expiration
- The change in diaphragmatic thickness (ΔTDI) during spontaneous breathing from the functional residual capacity to VT with normal value TDI% >20% [13] was calculated as follows:

$$\Delta\,TDI\% = \frac{\text{End} - \text{Inspiration thickness} - \text{End} - \text{Expiration thickness}}{\text{End} - \text{Expiration thickness}} \times 100$$

- US measurements were performed three times with the best value chosen as representative of diaphragmatic thickness fraction.

Statistical analysis of the data

The statistical package STATA 13.1 (StataCorp Ltd., College Station, TX, USA) was used for analysis.

Descriptive statistics for continuous variables presented as median (first to the third quartile). The nonparametric Wilcoxon test (Mann–Whitney) used for the comparison of continuous variables. Associations between dichotomous variables were performed by the Chi-square test or Fisher's exact test, where appropriate. The impact of sepsis on diaphragmatic function and short- or long-term mortality was assessed by Kaplan–Meyer survival function estimates. p < 0.05 considered significant.

Results

Demographic data

Our study included 30 patients 10 of them were males (33.3%) and 20 females (66.7%) with a mean age of 71.87 ± 17.42 years (Table 1).

Table 1: Distribution of the studied cases according to demographic data

Total (n = 30)	No.	%
Sex		
Male	10	33.3
Female	20	66.7
Age		
Min.–Max.	29.0–100.0	
Mean ± SD.	71.87 ± 17.42	

Diaphragmatic function parameters; DE and the TDI% on admission and along the ICU stay assessment and their correlation with mortality and APHACE II

The DE measured by M mode US on admission, had a mean of 1.19 ± 0.68 cm while the DE average through the whole ICU stay had a mean of 1.21 ± 0.58 cm. The Mean of TDI% measured by B mode US on admission was 34.47 ± 22.45% and its average mean was 33.27 ± 15.37, illustrated in Table 2.

Table 2: Diaphragm DE and TDI% on admission and its average of every 48 h along with the ICU stay

Parameter	On admission	Average along with the ICU stay
DE		
Min.–Max.	0.16–2.70	0.13–2.28
Mean ± SD.	1.19 ± 0.68	1.21 ± 0.58
Median (IQR)	1.05 (0.6–1.7)	1.17 (0.7–1.68)
TDI%		
Min.–Max.	5.0–84.0	13.50–69.33
Mean ± SD.	34.47 ± 22.45	33.27 ± 15.37
Median (IQR)	26.50 (19.0–56.0)	32.20 (20.67–43.1)

ICU: Intensive care unit, DE: Diaphragmatic excursion, TDI%: Diaphragm thickening fraction.

Regarding the relationship between the DE and mortality, there was a statistically significant reverse relationship between mortality and the DE on admission to ICU and average levels of DE with a p-value of 0.005*, and 0.003*, respectively. The same was found between mortality and TDI% on admission to ICU with a p-value of 0.033* and the average levels of TDI% with a p-value of 0.003* (Table 3).

The ROC curve (Figure 1) is showing that the APACHE II in our study had a significant relation

Table 3: Correlation diaphragmatic function (DE, TDI%) on admission and average along the ICU stay to predict the mortality of the studied cases

Parameter	Mortality		U	p
	No (n = 15)	Yes (n = 15)		
DE				
On admission				
Min.–Max.	0.16–2.70	0.31–2.61	46.0*	0.005*
Mean ± SD.	1.48 ± 0.61	0.90 ± 0.63		
Median (IQR)	1.42 (1.2–1.8)	0.72 (0.5–1.0)		
Average				
Min.–Max.	0.13–2.28	0.35–1.87	41.0*	0.003*
Mean ± SD.	1.51 ± 0.57	0.91 ± 0.43		
Median (IQR)	1.53 (1.2–1.9)	0.84 (0.5–1.2)		
TDI%				
On admission				
Min.–Max.	10.0–84.0	5.0–69.0	61.50*	0.033*
Mean ± SD.	42.87 ± 24.17	26.07 ± 17.56		
Median (IQR)	36.0 (25.0–58.5)	24.0 (13.5–29.5)		
Average				
Min. Max.	20.67–64.50	13.50–69.3	41.0*	0.003*
Mean ± SD.	41.95 ± 11.5	24.59 ± 14.0		
Median (IQR)	42.0 (34.4–46.9)	22.0 (15.6–25.4)		

ICU: Intensive care unit, DE: Diaphragmatic excursion, TDI%: Diaphragm thickening fraction.

with mortality with p-value 0.001* with cutoff value >32 and area under the curve (AUC) 0.862*, sensitivity 80.0% and specificity 80.0%. Furthermore, the different diaphragmatic functions had as significant reverse relation to mortality as the average of TDI% was the most significant parameter to predict the mortality with the cutoff value ≤25.7% and AUC 0.880*, sensitivity 80.0% and specificity 93.33%, followed by the average DE with the cutoff value of ≤1.272 cm and AUC was 0.818* with sensitivity 86.67% and specificity 73.33%. Furthermore, the DE and TDI% on admission showed significant reverse relationship with mortality with AUC (0.796*, 0.727*), respectively. However, there was no significant difference between the four parameters regarding the association with mortality so any one of them could be used as a predictor of mortality. While
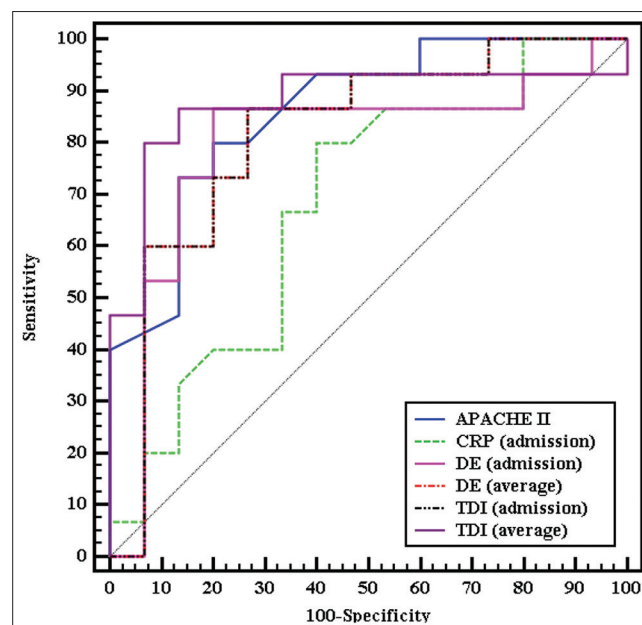

Figure 1: Receiver operating characteristic curve showing Correlation between acute physiology and chronic health evaluation II score, C-reactive protein, diaphragmatic function (Diaphragmatic excursions, Diaphragmatic Thickening Fraction) on admission and average along the intensive care unit stay to predict the mortality of the studied cases

CRP had no significant relation with mortality with p = 0.093 and AUC 0.680.
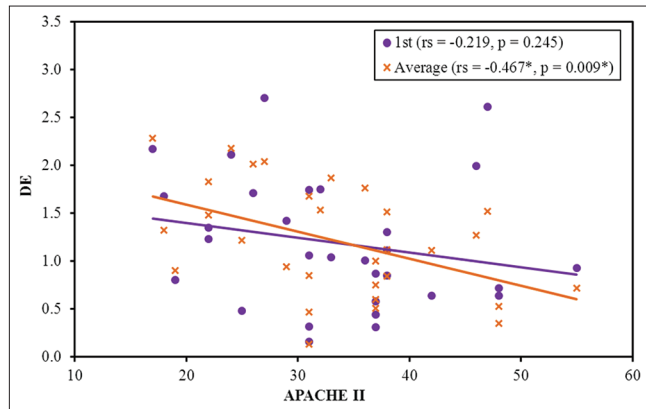

Figure 2: Correlation between Diaphragmatic excursions and the acute physiology and chronic health evaluation II score

In our study, there was statistically significant reverse relationship between APACHE II and the average of DE and TDI% along the ICU stay with p-value 0.009*, <0.001*, respectively while there was no statistically significant relationship between APACHE II and DE and TDI% on admission to ICU with p-value of 0.245, 0.051, respectively (Figures 2 and 3).
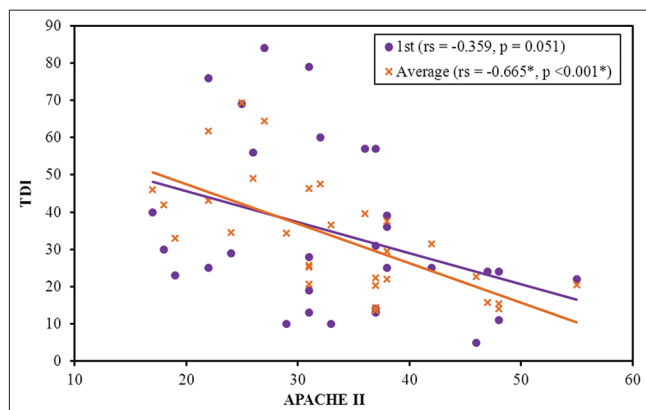

Figure 3: Correlation between Diaphragmatic Thickening Fraction and the acute physiology and chronic health evaluation II score

Correlation between the different diaphragmatic function parameters; DE and the TDI% in association with the need of MV and prediction of weaning from MV

A statistically significant reverse relation was found between the need of MV and the DE on admission to ICU with a p-value of 0.050*, also a significant reverse relationship between the need of MV and the average levels of DE with a p-value of 0.031*. However, there was no statistically significant relationship between the need of MV and the TDI% in the on admission to ICU with a p-value of 0.118 although the mechanically ventilated cases had a lower mean of 32.14 ± 23.17%. and there was no statistically significant relationship between the need of MV and the average levels of TDI% with a p-value of 0.078. Regarding the DE, there was a statistically significant reverse relationship

between the duration of MV and the DE on admission with a p-value of 0.017* and the average levels of DE along the ICU stay with a p-value of 0.007* (Figures 4 and 5). In addition, there was a statistically significant reverse relationship between the duration of MV and the TDI% on admission with a p-value of 0.041* and the average levels of TDI% along the ICU stay with a p-value of 0.015* (Figures 4 and 5).
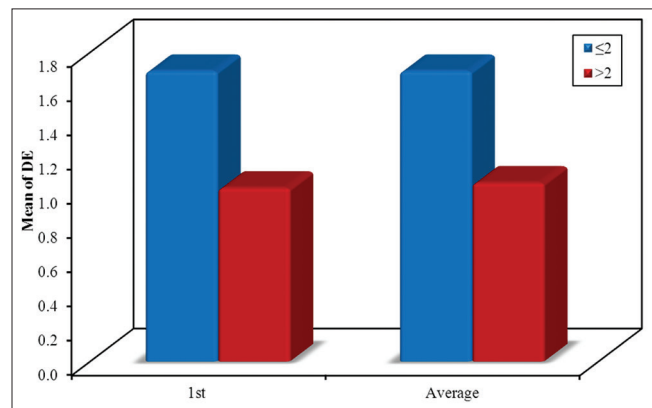

Figure 4: Correlation between Diaphragmatic excursions in association with the duration of mechanical ventilation

There was a statistically significant direct relationship between successful weaning from MV and the DE on admission to ICU with a p-value of 0.005* and the average levels of DE along the ICU stay with a p-value of 0.002*. In addition, the TDI% on admission to ICU had a statistically significant direct relation with MV successful weaning with a p-value of 0.033*, and the same relationship between the MV successful weaning and the average levels of TDI% with p-value of <0.001*(Figures 6 and 7).
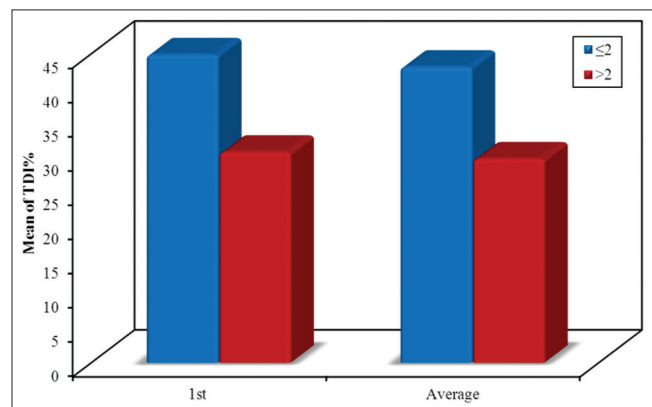

Figure 5: Correlation between Diaphragmatic Thickening Fraction in association with the duration of mechanical ventilation

The ROC curve in Figure 8 showed that the average of TDI% was the most significant parameter to predict successful weaning from MV with the cutoff value >25.66 and AUC 0.848*, sensitivity 87.50% and specificity 78.57% while the TDI% on admission showed cut off point >24 with sensitivity 75.0% and specificity 64.29%, the DE on admission and the average DE along the ICU stay with the cutoff value of >1.04, >0.84 cm and with sensitivity 87.50%, 87.50% and specificity 85.71%, 57.14%, respectively.
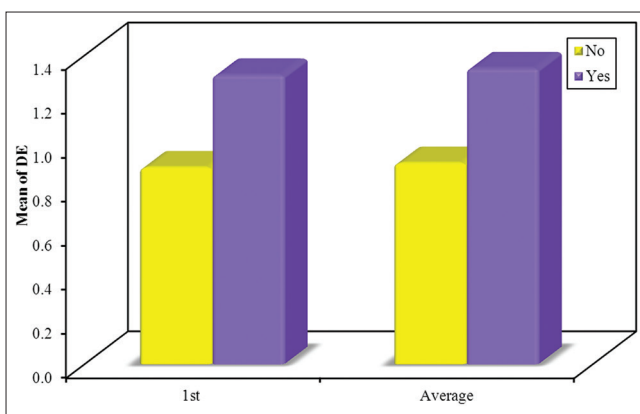
Figure 6: Correlation Diaphragmatic excursions in association with prediction of successful weaning from mechanical ventilation

Discussion

US is a safe and easy bedside imaging modality that could accurately evaluate the diaphragmatic functions in the ICU patients. In septic ICU patients, the mortality rate could be predicted by assessment of the diaphragmatic functions using US [6], [7]. Hence, this study aimed to evaluate the diaphragmatic function assessed by US in patients with sepsis and septic shock admitted to ICU along their ICU stay with correlating the diaphragmatic function assessed by US with the inflammatory marker CRP, sepsis severity and ICU length of stay, in-hospital mortality, duration of MV and successful weaning from MV.
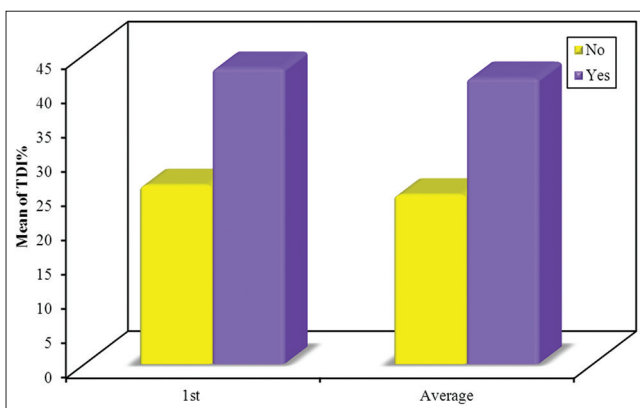

Figure 7: Correlation between the Diaphragmatic Thickening Fraction in association with prediction of successful weaning from mechanical ventilation

In our study, there was a statistically significant reverse relationship between mortality and the values of the DE and the TDI% on admission to ICU and their average along the ICU stay. This result was consistent with Mariani *et al*. [2], who assessed the diaphragmatic functions in 34 ICU patients during weaning trials using US. The US examination was performed by two blinded ultrasonographers who evaluated each hemi diaphragm during a spontaneous breathing trial. The diaphragmatic dysfunction (DD) was detected in 38% of patients on both sides with a higher ICU mortality rate in patients with DD (37% vs. 5%, p ¼ 0.048).

Although our study showed that the average of TDI% with B mode was the most significant parameter to predict the mortality more than average DE by M-mode, there was no significant difference between them. That was in disagreement with Mariani *et al*. [2], where DE with M-mode had better reproducibility.

In an observational, prospective study, Abdelhafeez *et al*. [16] evaluated the role of diaphragm in the weaning outcome also with assessment of the weaning process by looking to the duration of ventilation, the time needed for weaning and the length of ICU stay, re-ventilation and the patient's final fate. The findings of the study were similar to our results that showed lower statistically significant values of all sonographic measurements in relation to mortality.
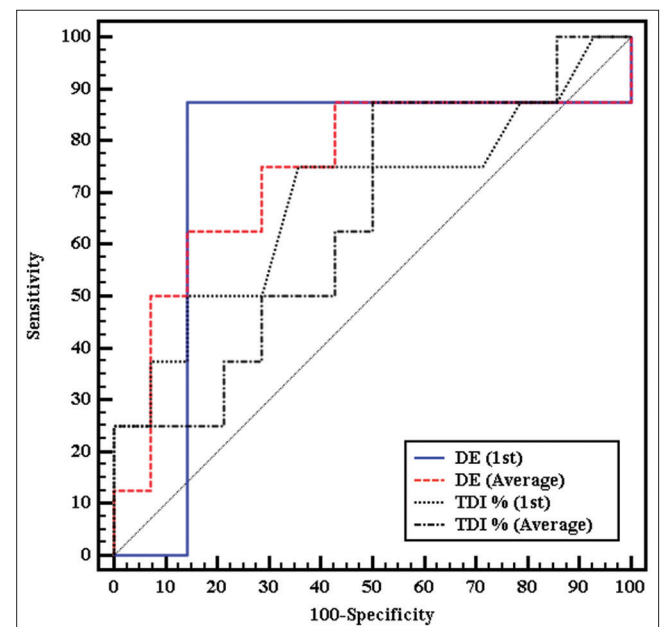

Figure 8: Receiver operating characteristic curve for different parameters to predict successful weaning from mechanical ventilation

The same was found by measuring the transdiaphragmatic twitch pressure (PdiTw) in response to bilateral magnetic stimulation of the phrenic nerves in Supinski and Callahan [17], they assessed the diaphragm strength in mechanically ventilated medical ICU patients. The study showed that the patients with severe diaphragm weakness (PdiTw <10 cmH2O) had poor outcomes, with evidently high mortality (49%) compared to patients with PdiTw ≥10 cmH2O (7% mortality, p = 0.022).

In addition, there was a statistically significant reverse relationship between APACHE II and the average of DE and TDI% along the ICU stay. This was agreed with Demoule *et al*. [3], a study that concluded the DD is a common finding on ICU admission. If DD associated with sepsis and severe illness as high APACHE II suggested a very poor prognosis.

In our study, the DE on admission to ICU had statistically significant reverse relation with the need of MV, Also a statistically significant reverse relationship between the need of MV and the average levels of

DE. Although, the mechanically ventilated cases had a lower mean of 32.14 ± 23.17% while the non-ventilated patients had a mean value of 40.88 ± 20.31% of the TDI% on admission, however, it was not statistically significant with p-value of 0.118, the same for the average levels of TDI% along the ICU stay with p-value of 0.078. In agreement with Goligher *et al*. [18], who studied the diaphragmatic activity using the US in mechanically ventilated patients. They measured the diaphragm thickness TDI and thickening fraction TDI% to detect the actual cause of diaphragmatic thickening whether the passive inflation by the ventilator or the inspiratory effort. They found a significantly lower TDI% in ventilated patients with a p-value 0.0001. Besides, this was consistent with, Lu *et al*. [19], who stated that the DD is earlier and more severe in mechanically ventilated patients with sepsis than the patients without sepsis.

This was in agreement with Ali and Mohamad [20]; they measured diaphragm thickness and excursion by US to predict the weaning consequences. There was a statistically significant reduction in the Mean of Diaphragmatic thickness, TDI%, and Mean of DE to long duration of MV. They stated that the incidence of maximum diaphragmatic changes occurred within 3 days after MV. The cutoff values of diaphragmatic US parameters predicting successful weaning were mean Diaphragmatic thickness >2 mm, diaphragmatic thickness fraction >30% and DE >1.5 cm.

Similar findings were found in the current study where a significant reverse relationship between the duration of MV and the DE and the TDI% on admission to ICU and average levels through the ICU stay. In addition, a statistically significant direct relationship between successful weaning from MV and both the DE, TDI% on admission to ICU, and with the average of DE and TDI% through the ICU stay. In addition, the average of TDI% along the ICU stay was the most significant parameter to predict successful weaning from MV with the cutoff value >25.66% and AUC 0.848*, sensitivity 87.50% and specificity 78.57%.

Agreed with Soliman *et al*. [21], where they studied the chest US to calculate the lung US (LUS) score and diaphragm US to measure TDI% in 100 invasive ventilated patients once they shifted to Spontaneous breathing trail and aimed to assess the weaning failure from MV, It found that TDI% can predict successful weaning with the cutoff value ≥29.5 with sensitivity 88.0% and specificity 80.0% with a p-value < 0.001 while LUS score can predict weaning failure by with cutoff value ≥15.5 with sensitivity 70.0% and specificity 82.5%.

In agreement with Zambon *et al*. [22], Ferrari *et al*. [23] and Eltrabili *et al*. [24]. The current study concluded the importance and accuracy of US to assess the diaphragmatic functions in the ICU septic patients. It could be used to predict extubation consequences, to detect respiratory failure, and to assess the atrophy in mechanically ventilated.

The limitation of this study

- The small sample size that may have a negative effect on the power of our statistics. So, further research with a larger group of patients is recommended to provide more accurate results
- Another concern was that diaphragmatic US like any other US is depended on the operator, image quality, patients' position, and anatomical variation
- Besides, sepsis and septic shock have a wide range of severity and usually associated with different comorbidities which may affect the power of different muscles including the diaphragm
- Finally, the inaccessibility to compare the diaphragmatic function assessed by the US to the gold standard means such as the PdiTw in response to bilateral magnetic stimulation of the phrenic nerves [3], [25].

Conclusion

The diaphragmatic function assessed by US could be used as a prognostic parameter in septic patients admitted to ICU. The different diaphragmatic function parameters (DE on admission, average DE, on admission TDI% and average TDI%) assessed by US could successfully assess the need, duration, and weaning from MV for ICU septic patients. In addition, diaphragmatic parameters could be used as a predictor of mortality in those patients.

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