sciendo Acta Marisiensis - Seria Medica 2022;68(3):103-107 DOI: 10.2478/amma-2022-0014

RESEARCH ARTICLE

Computed tomography evaluation of diaphragm alterations in 20 critically ill COVID-19 positive patients

Oana Elena Branea[1*], AnaMaria Romina Budeanu[2], Răzvan Gabriel Budeanu[3], Adrian Ștefan Chiuzan[4], Ioana Lăcrămioara Nazaret[5], Sanda Maria Copotoiu[1], Alexandra Elena Lazăr[1]

1. Department of Anesthesia and Intensive Care, George Emil Palade University of Medicine, Pharmacy, Science, and Technology of Târgu Mureș, România
2. Department of Anesthesia and Intensive Care, Emergency Clinical County Hospital of Târgu Mureș, România
3. Department of Radiology, Emergency Clinical County Hospital of Târgu Mureș, România
4. Department of Radiology, Emergency Clinical County Hospital of Bistrița, România
5. Department of Anesthesia and Intensive Care, Emergency Clinical County Hospital of Piatra Neamț, România

Objective: Diaphragmatic dysfunctions are multiple and critical illnesses often lead to the muscular atrophy that affects respiratory and peripheral muscles. The primary objective was to investigate diaphragm thickness in hospitalized patients. Secondary objectives were to assess clinical evolution and outcome. **Methods**: In a mean time period of 7.9 days, two different chest computed tomographies were used in order to examine diaphragm alterations of right and left diaphragm in 20 critically ill patients tested Real-Time Polymerase Chain Reaction positive to Severe Acute Respiratory Syndrome Coronavirus-2. Patients were divided in two groups (one group <5% decrease in diaphragm thickness and another group ≥5% decrease in diaphragm thickness). **Results**: Results showed that patients presented low 10 years predicted survival rate (Charlson Comorbidity Index > 7.7±3.08), marked inflammatory status (C-Reactive Protein = 98.22±73.35, Interleukine-6 = 168.31±255.28), high physiologic stress level (Neutrophil/Lymphocyte Ratio = 31.27±30.45), respectively altered acid-base equilibrium. Half of the investigated patients had decrease in diaphragm thickness by at least 5% (right diaphragm = -7.83%±11.11%, left diaphragm = -5.57%±10.63%). There were no statistically significant differences between those with decrease of diaphragm thickness and those without diaphragm thickness, regarding length of stay in Intensive Care Unit and in hospital, inflammatory markers, and acid-base disorders. **Conclusions**: Patients were admitted in Intensive Care Unit for acute respiratory failure and half of the investigated patients displayed diaphragm alterations at CT scan.

Keywords: diaphragm changes, chest computed tomography, critically ill, COVID-19

Received 4 May 2022 / Accepted 27 June 2022

Introduction

Background on causes of diaphragm changes and dysfunction

The diaphragm muscle plays multiple roles in our body by anatomically separating the thoracic cavity from the abdominal cavity and physiologically being the main inspiratory muscle [1]. Diaphragmatic dysfunctions are diverse and include paralysis that may be unilateral or bilateral. Unilateral diaphragmatic paralysis is generally asymptomatic if there are no other associated comorbidities, such as obesity and underlying lung disease. These cases are often diagnosed either by chest radiography, where a higher hemidiaphragm can be noticed, or by measuring the lung volume which can be decreased especially in case of bilateral paralysis. Neuromuscular weakness is another common pathology of the diaphragm. The causes of these dysfunctions can be found in Guillain-Barré syndrome, cardiogenic shock, ventilator-induced rhabdomyolysis, neuropathy and myopathy, which are common in critically ill patients. Apart benign or malignant tumors, injuries such as car accidents, shooting or cutting also jeopardize the diaphragm. The right hemidiaphragm is more prone to rupture, while the left hemidiaphragm is more likely to be affected during abdominal trauma. Another range of diaphragmatic pathologies are diaphragmatic hernias, often found in children and adults [2].

Clinical importance of diaphragmatic thickness assessment techniques

Pathologies of the diaphragm muscle are often detected by various imaging methods. Chest x-rays can detect a change in position or shape. Investigations such as computed tomography (CT) and Magnetic Resonance Imaging (MRI) may describe structural defects, intrinsic and adjacent pathology. Diaphragmatic thickness can be easily measured by using a CT scan and has an important role in determining the success of the diaphragm pacing system in amyotrophic lateral sclerosis (ALS) patients [3], assessing the diaphragmatic atrophy caused by mechanical ventilation (MV) or sepsis [4,5] and diagnosing ~~of~~ unilateral diaphragm paralysis [6]. Fluoroscopy is a major radiological means of evaluating diaphragmatic movements, although lately ultrasonography has become a simpler and more convenient method of evaluating the diaphragm [7]. Diaphragm ultrasonography is an accurate method for assessing dysfunction, it can predict the success or failure of extubation in critically ill patients, can quantify respira-

* Correspondence to: Oana Elena Branea
E-mail: branea_oana@yahoo.com

tory effort and detect atrophy. In addition, diaphragmatic ultrasonography in mechanically ventilated patients allows for repeated measurements over time, such as before and after variations of ventilator settings or before and after the onset of noninvasive ventilation [8].

Diaphragm alterations in critically ill

Critical illnesses often lead to ~~the~~ muscular atrophy that affects respiratory and peripheral muscles. The underlaying pend on multiple pathophysiological mechanisms, such as mitochondrial dysfunction, microvascular alterations or even changes in ionic homeostasis [9]. In critically ill patients, the diaphragm is often functionally impaired. Even though MV is a lifesaver intervention in critical patients, it predisposes to addiction and the chances for ventilator weaning being low, atrophy of the diaphragm can occur [10]. Diaphragm dysfunction during MV is caused by a variety of factors, such as sepsis, medication or even multiorgan dysfunction syndrome. Patients with Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-COV2) in Intensive Care Unit (ICU) require even more MV, weaning is further difficult, so that diaphragm changes are more common [11]. Alongside inflammation, a variety of factors are involved in this type of patients, the most important being critical myopathy, phrenic nerve injury and post-infectious inflammatory neuropathy of the phrenic nerve.

Materials and methods

Study Design and Objectives

We conducted a retrospective, single center study in the ICU of the County Emergency Clinical Hospital of Târgu Mureș. We aimed to obtain information on diaphragm changes in COVID-19 positive critically ill patients. The primary outcome was to investigate diaphragm thickness in hospitalized patients by using two different CT scans for each patient. The secondary outcomes were to examine the clinical courses of critically ill COVID-19 positive patients and the association between the degree of diaphragm changes and the in-hospital outcome.

Patients' features

Inclusion criteria comprised critically ill patients tested Real-Time Polymerase Chain Reaction (RT-PCR) positive for SARA-COV2, over 18 years old, having two thoracic CT scans in dynamic. We examined patients hospitalized between August 2021 and November 2021. -Children and pregnant women were excluded. We distributed the subjects in two groups: patients having <5% alterations in thickness and patients ≥ 5% decrease in thickness. All patients were diagnosed and treated according to the national guidelines and agreements.

Ethical Approval

This study was approved by the Research Ethics Committee of County Emergency Clinical Hospital of Târgu Mureș (No. 12964/ 20.05.2021 and No. 3249/ 04.02.2022).

Data Collection

Data were retrieved from the hospital's electronic medical record system (Hipocrate – H3) and patients' charts. Information included demographic and clinical characteristics, laboratory test results, imaging findings (RadiAnt DICOM Viewer program for CT analyses), and outcome. The information was then recorded in a pre-designed format of a Microsoft Excel table. All the data analyzed were collected as part of diagnosis and treatment by four investigators and further CT scans were examined by two radiologists. Regarding imaging, dynamic assessment of crural diaphragm thickness by chest CT was done. As seen in Figure 1 and Figure 2, the thickness of the right and left crural hemi diaphragms were measured at the level of the origin of the celiac artery, using an axial imaging.

Statistical Analyses

Data were statistically analyzed using Microsoft Office Excel and IBM SPSS Statistics 26. Data are mean ± standard deviation, unless otherwise stated. An independent-sample t-test and Mann-Whitney U test were run to detect statistical differences, after assessing normality distribution by the Shapiro-Wilk's test. A Spearman's rank-order correlation

Fig. 1. Axial CT at the level of celiac artery origin in the RadiAnt DICOM Viewer

Fig. 2. Diaphragmatic crus measured at the level of celiac artery origin; Celiac max length of each crus was determined as described by Sukkasem et al. [6]

was run to assess the relationship between data. Spearman's rho was interpreted as it follows for both positive and negative values: 0 - 0.299 no correlation, 0.3 – 0.499 weak correlation, 0.5 – 0.699 moderate correlation and 0.7 – 1 strong correlation. A two-sided P < 0.05 was considered statistically significant.

Results

The baseline characteristics of our 20 patients - 5 women and 15 men with a mean age of 68.90 ± 26.92 years are depicted in Table 1. In order to predict long term mortality, the Charlson Comorbidity Index (CCI) was calculated at the admission in the ICU with a mean of 7.70 ± 3.08. Length of stay in the hospital (LOS) was 14 ± 7.24 and they spent 8.9 ± 8.53 days in the ICU. As all of them were admitted for acute respiratory failure, patients needed oxygen therapy delivered through standard face masks or masks with reservoir bags for 17.55 ± 37.70 hours (range 0 -120 hours), non-invasive ventilation (NIV) for 62.10 ± 90.32 hours (range 0 – 244 hours) and MV for 132.95 ± 210.42 hours (range 0-846 hours). Thickness assessment of diaphragm by CT scans in dynamic – the mean time between CT scan1 and CT scan 2 was 7.9 days - showed that the right diaphragm was altered by -7.83 ± 11.11% and the left diaphragm by -5.57 ± 10.63% in half of the patients. There was a remarkable uniformity of the two groups studied (Table 2), with no statistically significant difference in age (p=0.490), CCI (p=0.575) or length of stay (LOS) in hospital (p=0.161). Patients whose diaphragm decreased in thickness, needed a longer period of oxygen therapy (p=0.043). Moreover, as presented in Table 7, we found a weak correlation between MV and the right diaphragm thickness (Spearman's rho = 0,418, p= 0,067), between the right diaphragm thickness and NIV (Spearman's rho = -0.314, p=0,177), and a very weak correlation between the right diaphragm thickness and oxygen therapy (Spearman's rho = -0.175, p=0.490). There appeared to be no statistical difference at all.

Laboratory biomarkers were analyzed as shown in Table 3. High NLR=31.27±30.45 levels, high CPR levels of 98.22 ± 73.35 mg/dl and high values of Il-6=168.31 ± 255.28 characterized our study population. Hyperfibrinolysis (502.75 ± 180.36) and hyperferritinemia (17770.20 ± 1518.78) were also found. As presented in Table 4., we noticed no statistically significant difference between patients with <5% change in thickness compared to ≥ 5% decrease in thickness regarding NLR (p= 0.579), CRP (p= 0.055), IL-6 (p= 0.905), ferritin (p= 0.454), and fibrinogen (p= 0.977). The closest biomarker to a statistical significance was CRP.

As seen in Table 5., variations of pH, A-a PO2 gradient, a/A ratio, respiratory index (RI), and Horowitz index suggested damage of the pulmonary function in the studied group. Still, all patients presented ventilation-perfusion

Table 1. Demographic and clinical characteristics

Characteristics	Mean	SD	Min.	Max.	95% CI for mean
Age (years)	68.90	26.92	27	89	60.98 - 76.82
CCI	7.70	3.08	2	14	6.26 -9.14
LOS in hospital (days)	14.00	7.24	5	38	10.61-17.39
LOS in ICU (days)	8.9	8.53	1	38	4.90 -12.90
MV (hours)	132.95	210.42	0	846	34.46 -231.43
NIV (hours)	62.10	90.32	0	244	19.86 -104.33
Oxygen therapy (hours)	17.55	37.70	0	120	-0.09 -35.19
Right diaphragm difference CTscan2 – CT scan1 (%)	-7.83	11.11	-37.93	4.76	-13.03 - -2.62
Left diaphragm difference CTscan2 – CT scan1 (%)	-5.57	10.63	-42	6	-10.54 - -0.59

Table 2. Clinical differences in the two groups - changes in diaphragm thickness <5% change in thickness compared to ≥5% decrease in thickness

Characteristics	p value (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference
Age (years)	0.490	5.400	7.671	-10.716 – 21.516
CCI	0.575	0.800	1.402	3.746
LOS in hospital (days)	0.161	-4.600	3.149	-11.215 – 2.015
Oxygentherapy (hours)	0.043	-5.300	2.436	-10.418 - -0.182

Table 3. The inflammatory response of the critically ill Covid 19 positive patients

Characteristics	Mean	SD	Min.	Max.	95% CI for mean
Neutrophil/ Lymphocyte Ratio (n=20)	31.27	30.45	7.30	137.22	17.02 – 45.52
Fibrinogen (mg/dl) (n=14)	502.75	180.36	182.00	743.59	398.61 – 606.89
Ferritin (ng/ml) (n=14)	17770.20	1518.78	1623	4883	398.61 – 606.89
CRP(C-reactive protein) (mg/dl) (n=18)	98.22	73.35	14.90	287.89	59.26 – 137.19
IL-6 (interleukin-6) (pg/ml) (n=9)	168.31	255.28	1.50	1105.00	-104.73 – 441.37

Table 4. Biomarkers differences in the two groups - Changes in diaphragm thickness <5% change in thickness compared to ≥ 5% decrease in thickness

Characteristics	p value (2-tailed)
Neutrophil/ Lymphocyte ratio	0.579
Fibrinogen	0.977
Ferritin	0.454
IL-6 (interleukin-6)	0.905
CRP (C-reactive protein)	0.055

Table 5. Acid- base disorders

Characteristics	Mean	SD	Min.	Max.	95% CI for mean
pH	7.25	0.19	6.80	7.50	7.15 – 7.35
paO2 (mmHg)	97.75	64.62	36	295.6	65.61 – 129.89
paCO2 (mmHg)	44.43	22.88	21.8	116.0	32.96 – 55.72
A-a (mmHg)	372	192.52	-46	628	274.0 – 471.97
a/A	0.39	0.59	0.10	2.4	3.12 – 6.77
RI	4.95	3.55	-0.3	12.3	3.12-6.77
P/F	213.90	282.42	46.5	1143.0	73.45 – 345.35

Table 6. Acid-base differences in the two groups – decrease in diaphragm thickness of <5% versus ≥5% decrease in thickness

Characteristics	P value (2-tailed)	Mean Difference	Std. Error Difference	95% CI for mean
pH	0.641	0.04556	0.09585	-0.15763 – 0.284274
A-a	0.806	-24.0819	96.4173	-229.5906 – 181.42
RI	0.853	0.3361	1.7798	-3.4575 – 4. 1297

Table 7. Correlations between right diaphragm alterations and MV, NIV and oxygen therapy

		MV	NIV	Oxygen therapy
Right diaphragm difference CT scan2 – CT scan1	Spearman's rho	0.418	-0.314	-0.175
	p value (2-tailed)	0.067	0.177	0.460
	N	20	20	20

abnormalities (Table 6.), no statistically significant differences were noticed between patients with <5% change in thickness compared to >=5% decrease in thickness, regarding pH (p=0.641), A-a O2 (p=0.806), RI (p=0.684).

Discussions

Little information is provided by the medical literature to describe diaphragm changes in COVID-19 critically ill patients. When searching on PubMed the "diaphragm dysfunction COVID-19 critically ill" engram by 21April 2022, we found only three articles. In response to our primary outcome, results showed that right diaphragm decreased in thickness by 7.83% and left diaphragm by 5.57% in a mean time of approximately 9 days. Inflammatory markers showed that patients responded to COVID-19 infection by a cytokine storm. NLR shows a dynamic relationship between neutrophils and lymphocytes and it may be influenced by several conditions, such as: age, chronic comorbidities, medication and stress). Yet as Zahorec presents in his study, in critically ill patients a higher value than 9 is expected to characterize these patients [12]. A rapid increase in NLR was observed in our study, reflecting a high physiologic stress. The high levels of CRP we noticed in our subjects were interpreted as signs of hyperactivity of the immune systems. In 2020, Nurshad published results indicating that elevated levels of CRP could be a marker for the severity of COVID-19 [13]. As suggested by Jyoti Shekhawat, IL-6 was found to predict disease prognosis and deterioration of clinical profile [14]. This seems to be the case in our study too. These markers were proposed to describe complicated diseases with immune dysregulation, contributing to the cytokine storm syndrome [15]. Biomarkers response contributed to the cytokine storm and followed the same path for all critically ill. Frequent acid-base alterations were expected in COVID-19 critically ill patients admitted, notably metabolic and respiratory alkalosis, as Gaetano Alfano published in one of the first studies regarding acid-base disorders in COVID-19 patients [17]. We need to emphasize ~~mentioned~~ that another tool used in the assessment of diaphragm thickness is ultrasonography. During 2013 and 2016, Goligher investigated by ultrasonography 222 critically ill patients. Compared to those without changes in diaphragm thickness, those with decrease in diaphragm thickness during the first week of MV, had a significantly lower incidence of liberation of mechanical ventilation at day 21 [18]. Diaphragm monitoring by ultrasound could be of help in weaning form mechanical ventilation. It could be particularly useful in patients presenting difficult and prolonged weaning and could help diagnose diaphragm dysfunction that can interfere with the weaning process. It seemed to work as a predictor of extubation failure and was used to implement appropriate preventive strategies [19]. Diaphragm monitoring may be used to tailor the ventilator settings in order to provide diaphragm protective ventilation – between over and under diaphragm use.

Limitations and possible benefits of the present study

Despite the impact that CT scan analysis of diaphragm in COVID-19 positive critically ill patients may have, the findings of this study have to be seen cautiously. There are certain limitations of our study. The published research on this topic is scarce, which gives room to either groundbreaking results or to very disappointing ones. Still, if cautiously and steadily used, our approach might qualify for the routine diaphragm monitoring and play as an important opportunity for further results in the area. The second concerns the sample study, that does not reflect the general population of COVID-19 positive critically ill patients. Moreover, the subjects were treated and studied in a single center – even if regional and comprising many referred patients. Although lung and diaphragm ultrasound are harmless and already a routine for some intensivists, thus a versatile and useful tool to examine in dynamic the performance of the diaphragm and its morphologic alterations, CT scans only to assess the diaphragm are a little too much. We only used the data provided by CT scans done as indicated by the intensivists and included in the therapeutic protocols for respiratory failure of the Covid 19 patients. But in order to quantify better the diaphragm changes and to draw valid conclusions, the field of research is largely opened and unoccupied.

Conclusions

In our study, COVID-19 hospitalized patients in ICU presented low 10 years predicted survival rate, marked inflammatory status, high physiologic stress level, respectively altered acid-base balance. Half of the investigated patients presented decrease in diaphragm thickness, by at least 5%. There were no statistically significant differences between those with decrease of diaphragm thickness and those without decrease in diaphragm thickness, regarding LOS in ICU and LOS in hospital, MV and NIV, inflammatory markers, and acid-base disorders. Also, there were weak correlations between diaphragm alterations and different types of oxygentherapy, NIV, MV. Still, on the long run, the predicted survival is to be confirmed or infirmed. So appears to be the significance of the diaphragm morphologic decay. Monitoring diaphragm function in the ICU could lead physicians to a better understanding of the interaction between the patient's effort and the ventilator.

Author Contributions

O-EB: Conceptualization, Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing
ARB: Data curation, Methodology, Writing – original draft
RGB: Data curation, Investigation, Formal Analysis, Writing – original draft
AȘC: Data curation, Investigation, Writing – original draft
ILN: Data curation, Investigation, Writing – original draft
SMC: Supervision, Validation, Visualization, Writing – review & editing
AEL: Supervision, Validation, Visualization, Writing – review & editing
All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Conflict of Interest

None to declare.

References

1. Kocjan J, Adamek M, Gzik-Zroska B, Czyżewski D, Rydel M. Network of breathing. Multifunctional role of the diaphragm: a review. Adv Respir Med. 2017;85(4):224-232.
2. McCool FD, Manzoor K, Minami T. Disorders of the Diaphragm. Clin Chest Med. 2018;39(2):345-360.
3. Sanli A, Sengun IS, Tertemiz KC, Alpaydin AO, Karacam V, Sanli BA, et al. Importance of diaphragm thickness in amyotrophic lateral sclerosis patients with diaphragm pacing system implantation. Surg Endosc. 2016;30: 154-8.
4. Lee GD, Kim HC, Yoo JW, Lee SJ, Cho YJ, Bae K, et al. Computed tomography confirms a reduction in diaphragm thickness in mechanically ventilated patients. J Crit Care. 2016;33:47-50.
5. Jung B, Nougaret S, Conseil M, Coisel Y, Futier E, Chanques G, et al. Sepsis is associated with a preferential diaphragmatic atrophy: a critically ill patient study using tridimensional computed tomography. Anesthesiology. 2014;120:1182-91.
6. Sukkasem W, Moftah SG, Kicska G, Godwin JD, Pipavath S, Stern E. Crus atrophy: Accuracy of computed tomography in diagnosis of diaphragmatic paralysis. J Thorac Imaging. 2017;32: 383-90.
7. Koo CW, Johnson TF, Gierada DS, White DB, Blackmon S, Matsumoto JM, et al. The breadth of the diaphragm: updates in embryogenesis and role of imaging. Br J Radiol. 2018;91(1088):20170600.
8. Zambon M, Greco M, Bocchino S, Cabrini L, Beccaria PF, Zangrillo A. Assessment of diaphragmatic dysfunction in the critically ill patient with ultrasound: a systematic review. Intensive Care Med. 2017;43(1):29-38.
9. Vivier E, Roussey A, Doroszewski F, Rosselli S, Pommier C, Carteaux G, et al. Atrophy of Diaphragm and Pectoral Muscles in Critically Ill Patients. Anesthesiology. 2019;131(3):569-579.
10. Schepens T, Dres M, Heunks L, Goligher EC. Diaphragm-protective mechanical ventilation. Curr Opin Crit Care. 2019; 25(1):77-85.
11. Maslove DM, Sibley S, Boyd JG, Goligher EC, Munshi L, Bogoch II, et al. Complications of Critical COVID-19: Diagnostic and Therapeutic Considerations for the Mechanically Ventilated Patient. Chest. 2021;13:S0012-3692(21)04094-0.
12. Zahorec R. Neutrophil-to-lymphocyte ratio, past, present and future perspectives. Bratisl Lek Listy. 2021;122(7):474-488.
13. Nurshad A. Elevated level of C-reactive protein may be an early marker to predict risk for severity of COVID-19. J Med Virol. 2020;92(11):2409-2411.
14. Shekhawat J, Gauba K, Gupta S, Purohit P, Mitra P, Garg M, et al. Interleukin-6 Perpetrator of the COVID-19 Cytokine Storm. Indian J Clin Biochem. 2021;21;36(4):1-11.
15. Vargas-Vargas M, Cortés-Rojo C. Ferritin levels and COVID-19. Rev Panam Salud Publica. 2020;44:e72.
16. Long W, Yang J, Li Z, Li J, Chen S, Chen D, et al. Abnormal Fibrinogen Level as a Prognostic Indicator in Coronavirus Disease Patients: A Retrospective Cohort Study. Front. Med. 2021;8:687220.
17. Alfano G, Fontana F, Mori G, Giaroni F, Ferrari A, Giovanella S, et al. Acid base disorders in patients with COVID-19. Int Urol Nephrol. 2022;54(2): 405–410.
18. Goligher EC, Dres M, Fany E, Rubenfeld GD, Scales DC, Herridge MS, et al. Mechanical Ventilation – induced Diaphragm Atrophy Strongly Impacts Clinical Outcomes. Am J Respir Crit Care Med. 15;197(2):204-213.
19. Saccheri C, Morawiec E, Delemazure J, Mayaux J, Dubé BP, Similowski T, et al. ICU-acquired weakness, diaphragm dysfunction and long-term outcomes of critically ill patients. Ann Intensive Care. 2020;10(1):1.