

 ISSN NO. 2320-5407	Journal Homepage: - www.journalijar.com INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR) Article DOI: 10.21474/IJAR01/13525 DOI URL: http://dx.doi.org/10.21474/IJAR01/13525	 INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR) ISSN 2320-5407 Journal Homepage: http://www.journalijar.com Journal DOI: 10.21474/IJAR01
---	--	--

RESEARCH ARTICLE

THE HISTOLOGICAL EFFECTS OF COVID-19 ON THE LOWER RESPIRATORY SYSTEM

Ahmed Mead¹ and Mohamed Abdullahi Yusuf²

1. Faculty of Medicine, Department of Basic Medical Science, Salaam University, Mogadishu, Somalia.
2. Faculty of Medicine, Department of Internal Medicine, Somali National University, Mogadishu, Somalia.

Manuscript Info

Manuscript History

Received: 10 August 2021

Final Accepted: 14 September 2021

Published: October 2021

Key words:-

Respiratory Tract, Histology, Lung,
Covid-19, Diffuse Alveolar Damage
(Dad)

Abstract

Both histologically and anatomically, the respiratory system is a compound system having diverse functions. It fulfills the process of respiration that is regarded as gas exchange through conduction and filtration of air. The respiratory system is functionally divided into conducting and respiratory parts. Anatomically, the respiratory tract is categorized into the upper and lower respiratory tract. The lower respiratory tract represents the organs within the thorax such as the trachea, bronchi, bronchioles, alveolar duct, and alveoli which make up the lungs. The paired lungs are parts of the lower respiratory tract which are regularly presented microorganisms. Although COVID-19 affects different organs simultaneously; it seriously affects the lower respiratory system, produces respiratory distress to affected individuals, and mostly produces histological changes in the respiratory tract. In terms of COVID-19 effects on the lower respiratory tract, the lungs are affected in most cases, and the review is largely focused on the lungs. The histological effects of COVID-19 on the lungs are different and reveal a broad spectrum of abnormalities. Diffuse alveolar damage (DAD) remained the principal lung histopathological finding in patients with COVID-19. DAD results from damage of the covering cells of the alveoli and endothelium ending with disarrangement of the blood-air barrier. Concerning the event of pulmonary injury, DAD is classified into three histopathological stages that are acute (exudative), subacute (organizing), and chronic (fibrotic) stage. Since there is no adequate information about the histological effects of COVID-19 on the lower respiratory system, this article aimed to review what is known about the histological effects of COVID-19 on the lower respiratory system. It summarizes the previous literature of published articles that examined the histological effects of COVID-19 on the lower respiratory system to display the present understanding of histological changes of the lower respiratory system associated with COVID-19. Further data about the histological effects of COVID-19 on the lower respiratory system is needed to adequately define the histopathological changes of the lower respiratory system associated with COVID-19.

Copy Right, IJAR, 2021,. All rights reserved.

Corresponding Author:- Ahmed Mead

Address:- Faculty of Medicine, Department of Basic Medical Science, Salaam University, Mogadishu, Somalia.

Introduction:-

Both histologically and anatomically, the respiratory system is a compound system having diverse functions (Haschek, Rousseaux, and Wallig, 2010). It fulfills the process of respiration that is regarded as gas exchange through conduction and filtration of air (Ross, 2011). The respiratory system is divided into conducting and respiratory parts (figures 1 and 2). The conducting part starts from the nasal cavity to the nasopharynx, larynx, trachea, primary bronchi, secondary bronchi, tertiary bronchi and ends in the terminal bronchiole. The respiratory part begins from the respiratory bronchiole to the alveolar ducts, alveolar sacs, and alveoli which are the site of gas exchange. The respiratory bronchiole is the midway between the conducting and respiratory parts (figure 2) (Alkanlı and Koroglu, 2019).

Anatomically, the respiratory tract is categorized into the upper and lower respiratory tract. The lower respiratory tract represents the organs within the thorax such as the trachea, bronchi, bronchioles, alveolar duct, and alveoli which make up the lungs (Patwa and Shah, 2015). The paired lungs are parts of the lower respiratory tract which are regularly presented microorganisms. Fortunately, lungs possess a major character to identify the serious materials exposed to them (Alkanlı and Koroglu, 2019). Within these lungs, the airways bifurcate into frequently smaller tubes to give the smallest air spaces, called the alveoli. Alveoli are the most terminal segment of the respiratory passage. The groups of alveoli gathered collectively and having a common opening are termed as an alveolar sac. Alveoli that make a tube are termed as alveolar ducts (Ross, 2011).

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) appeared in late 2019, producing the disease coronavirus disease 2019 (COVID-19) (Brosnahan, Jonkman, Kugler, Munger, and Kaufman, 2020). The disease spread rapidly in China and brought many lives to death and created a rise in global cases. COVID-19 is severe in the elderly and in chronically ill individuals. Treatment was supportive to manage symptoms and complications, and vaccines for COVID-19 were not ready during that time. This gave COVID-19 global attention and World Health Organization declared COVID-19 as a global public health crisis (Mead, 2020). During this pandemic period, COVID-19 was accountable for a number of respiratory problems (Tamburello, Bruno, and Marando, 2020).

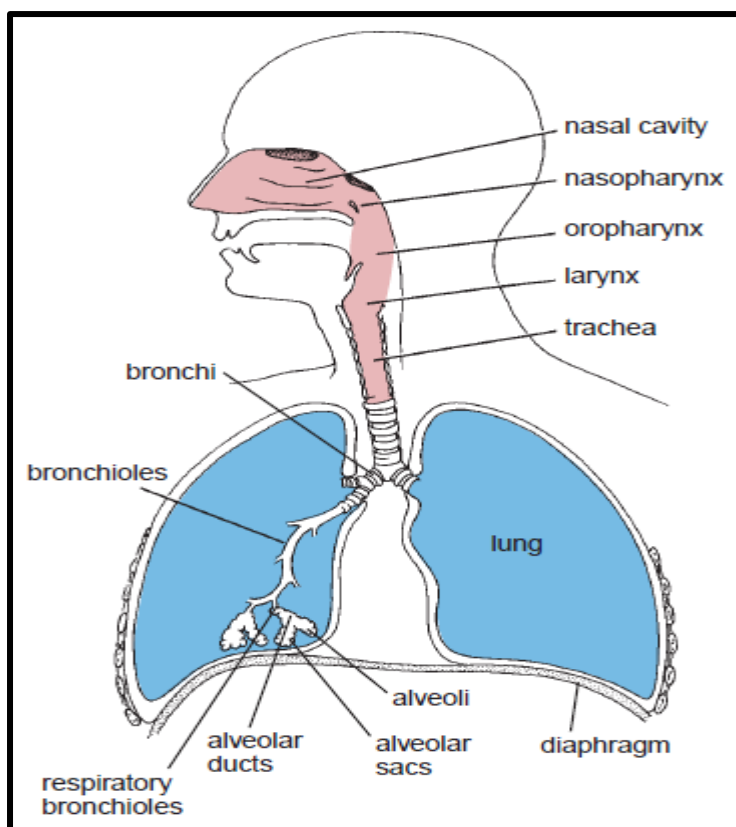


Figure 1:- Represents the respiratory passages of the respiratory system consisting of conducting and respiratory parts (Ross, 2011).

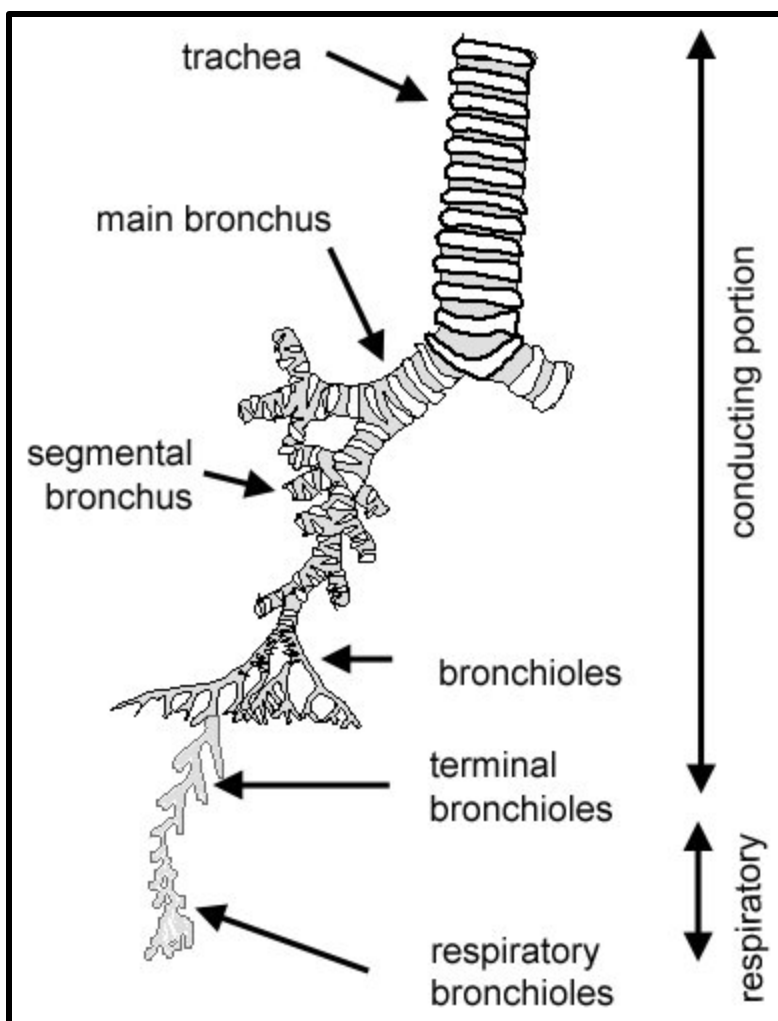


Figure 2:- The area of transition between conducting and respiratory parts (Alkanlı and Koroglu, 2019).

Normal Histological Structure of the Lower Respiratory System

The lower respiratory tract starts from the trachea to the paired lungs. The trachea and bronchi are lined by a pseudostratified epithelium (figure 3), where the ciliated columnar cell is the principal cell (French, 2009). The entire bronchi are enclosed by unique lung tissue (LT) manifesting blank spaces of lung alveoli. The epithelium is also lined by ciliated pseudostratified columnar in the larger bronchioles (figure 4); however, this diminishes in the smallest terminal bronchioles as well as respiratory bronchioles and begins to be ciliated simple columnar or simple cuboidal epithelium. The cuboidal epithelium of terminal and respiratory bronchioles consists chiefly of Clara cells. Respiratory bronchioles' distal ends (figure 5) divide into tubes termed as alveolar ducts which are fully lined by alveoli openings. The ends of the alveolar ducts are distally constituted by larger groups of alveoli which are termed as alveolar sacs (Mescher, 2013).

Alveoli are enclosed and isolated from each other by an extremely thin connective tissue layer that contains blood capillaries. A tissue known as the alveolar septum or septal wall separates neighboring alveolar air spaces. The alveolar epithelium is formed of type I and II alveolar cells that line the alveolar surface. Type I alveolar cells also called type I pneumocytes are thin squamous cells. Type II alveolar cells also known as type II pneumocytes or septal cells are secretory cuboidal cells that secrete surfactant. They are progenitor cells for type I alveolar cells and regenerate both types I and type II alveolar cells in the alveolus (Ross, 2011)(Davies and Moores, 2010).

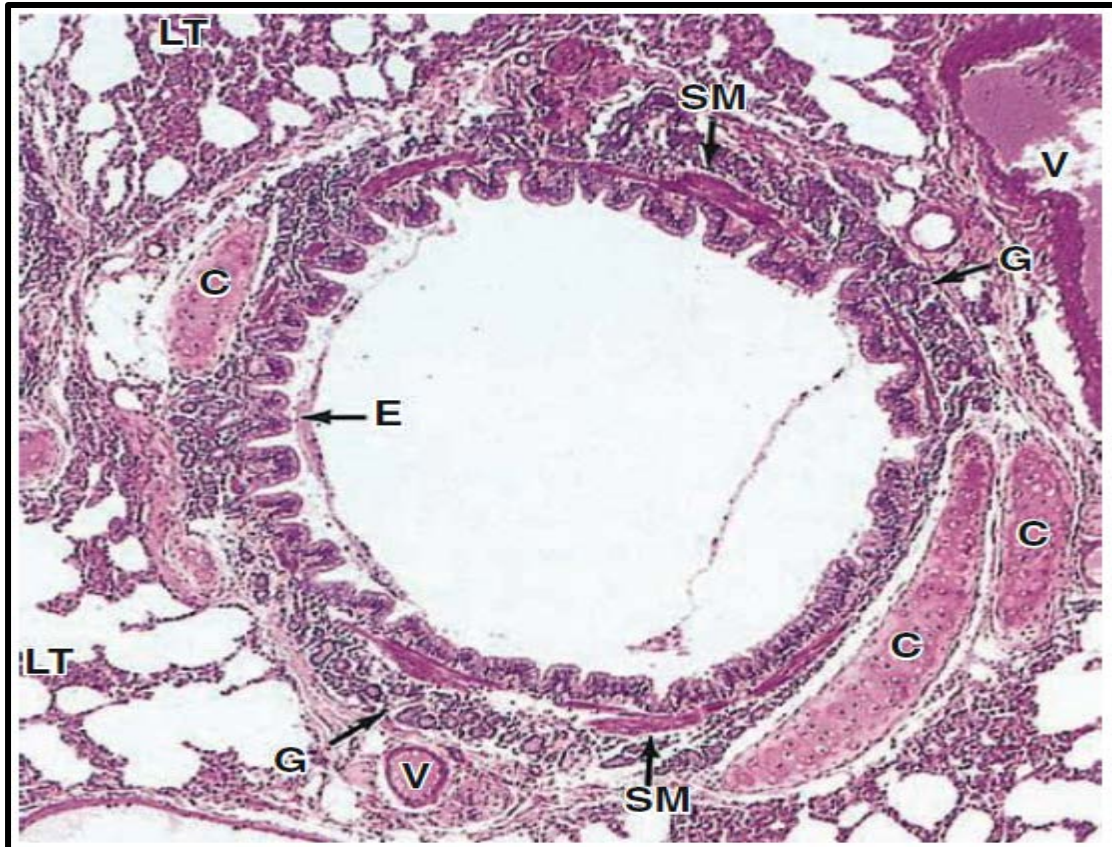


Figure 3:- A large bronchus, the lining of the pseudostratified epithelium (E). The entire bronchi enclosed by unique lung tissue (LT) shows blank spaces of lung alveoli. SM, Smooth muscle; C, Cartilage; G, Glands; V, veins (Mescher, 2013).



Figure 4:- A large bronchiole possesses pseudostratified epithelium (E) and smooth muscle (arrows), backed by connective tissue (CT) (Mescher, 2013).

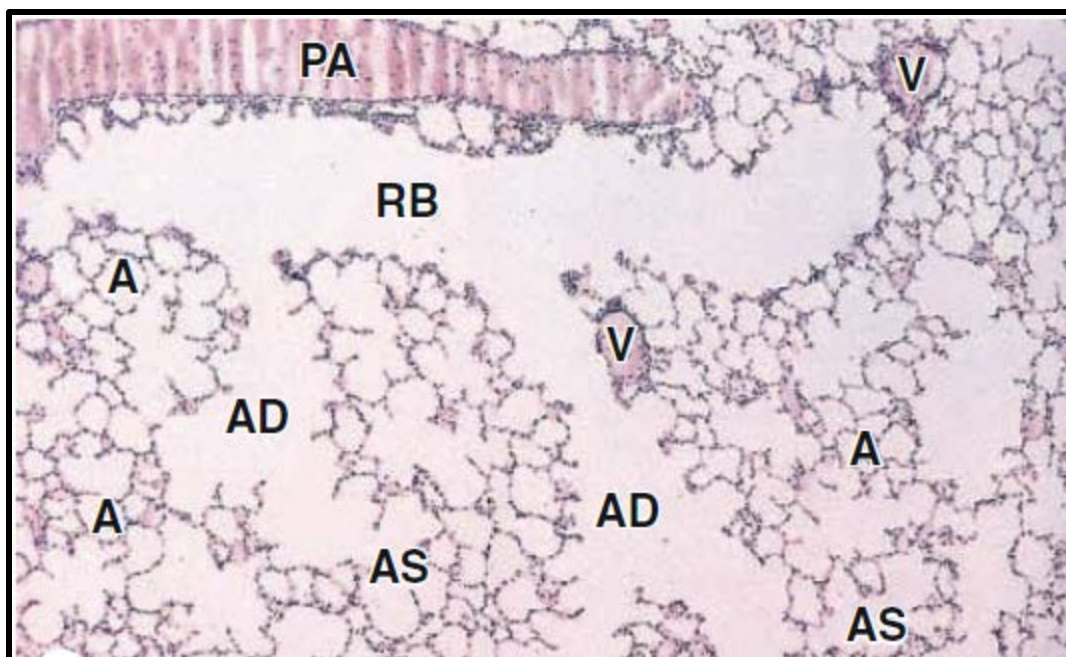


Figure 5:- Lung tissue. RB, respiratory bronchioles; AD, alveolar ducts; AS, alveolar sacs; A, alveoli; PA, pulmonary artery; V, vein (Mescher, 2013).

Histological effects of COVID-19 on the lower respiratory system

Although COVID-19 affects different organs simultaneously, it seriously affects the lower respiratory system, produces respiratory distress to affected individuals, and mostly produces histological changes in the respiratory tract (Alsaad, Arabi, and Hajeer, 2020; Rajaa and Nada, 2020). In terms of COVID-19 effects on the lower respiratory tract, the lungs are affected in most cases, and the review is largely focused on the lungs (Deshmukh, Motwani, Kumar, Kumari, and Raza, 2020). The histological effects of COVID-19 on the lungs are different and reveal a broad spectrum of abnormalities (Brosnahan et al., 2020).

Although the epithelium of the respiratory tract serves as a barrier to pathogens and protects the tissues from damage by mucus secretion, surprisingly, it is the principal position of the coronavirus entrance. COVID-19 damages the alveolar epithelium in a dispersed manner causing considerably weakened exchange in gases and respiratory failure (figure 6). In addition to alveolar damage, microscopic findings showed the development of hyaline membrane (figure 7A, B), thrombi, and edema. Dispersed type II alveolar epithelium hyperplasia was noted (figure 7C, E). Hemorrhage is observed in the lumen of alveoli with fibrin accumulation (figure 7D) (Brosnahan et al., 2020). Xu et al (2020) primarily displayed the histopathological changes of coronavirus infections. Changes observed include the destruction of the alveoli, interstitial infection, the presence of reactive pneumocytes, and syncytial cells (Alsaad et al., 2020).

In general, diffuse alveolar damage (DAD) remained the principal lung histopathological finding in patients with COVID-19. DAD results from damage of the covering cells of the alveoli and endothelium ending with disarrangement of the blood-air barrier. In relation to the event from pulmonary injury, DAD is classified into three histopathological stages that are acute (exudative), subacute (organizing), and chronic (fibrotic) stage. The acute stage of DAD (figure 9A) happens within one week of the primary injury and is delineated by intra-alveolar hyaline membranes, edema, and alveolar wall thickening in the absence of notable inflammation (Hariri et al., 2021).

The subacute phase (figure 9B) of DAD happens about one week following the primary pulmonary injury and is delineated by the microscopic structure of the fibrin accompanied by migration fibroblast and secretion of loose collagen. Hyaline membranes become slowly organized into organizing fibrotic tissue, which starts to be visible in airspaces, alveolar ducts, and alveolar walls. Unusual variations in type II pneumocytes and squamous metaplasia may be initiated. In a few situations, DAD finally resolves, whereas others develop into a chronic fibrotic phase

following weeks to months of the initial injury with increasing structural reconstruction and interstitial fibrosis (Hariri et al., 2021).

Acute fibrinous and organizing pneumonia (AFOP) is identified by the formation of fibrin balls inside the alveolar spaces. The organization follows the migration of fibroblast and the production of young collagen within fibrin aggregates (figure 9C). The appearance of hyaline membranes implies DAD. Organizing pneumonia (OP) is observed as isolation or in union with DAD or AFOP and is distinguished by intraluminal tufts of plump fibroblasts and immature tissue of collagen in alveolar ducts and distal airspaces (figure 9D) (Hariri et al., 2021).

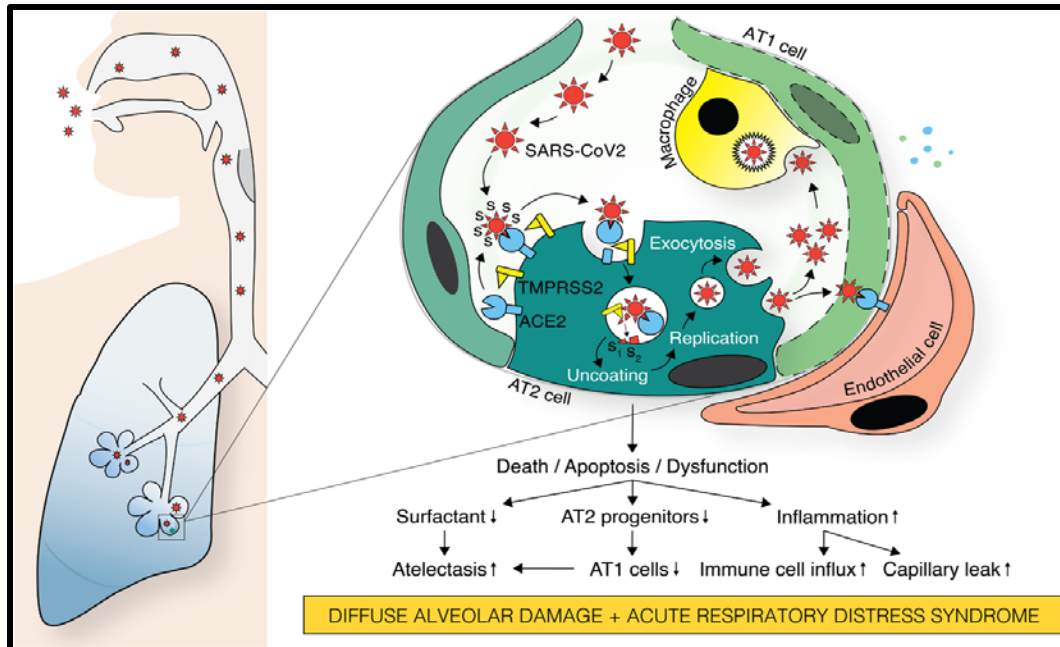


Figure 6:- How COVID-19 damages alveolar epithelium ACE2, angiotensin-converting enzyme-2; TMPRSS2, transmembrane serine protease 2; AT1, alveolar type I; AT2, alveolar type II (Brosnahan et al., 2020).

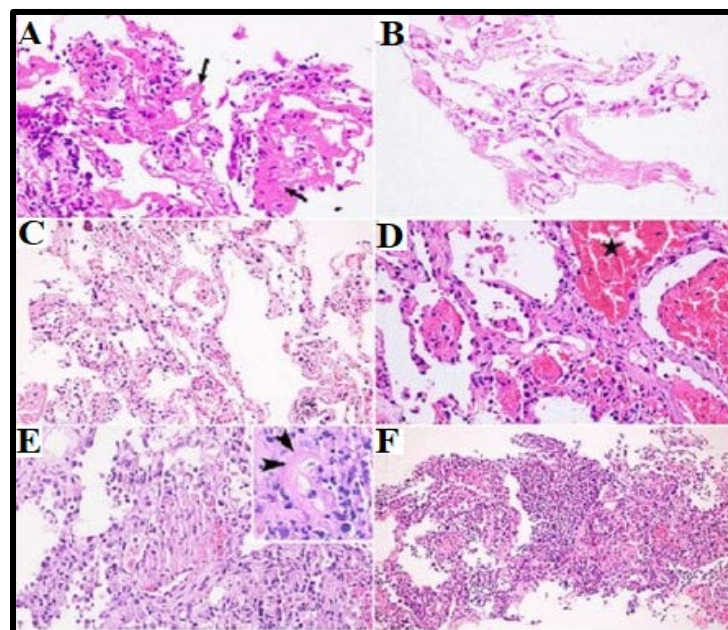


Figure 7:- (A, B, C, D, E, F) Histological changes of the lungs. (A) The lung is invaded by inflammatory cells combined with alveolar epithelium destruction and development of hyaline membrane (arrow). (B) Development of

hyaline membrane without invasion of inflammatory cells. (C) Type II alveolar epithelium hyperplasia and interstitial thickening are observed. (D) Hemorrhage is seen in the lumen of alveoli (asterisks) with fibrin accumulation. (E) The appearance of fibrinoid vascular necrosis (inset) and dispersed type II alveolar epithelium hyperplasia. (F) Invasion of the alveolar lumen by inflammatory cells mostly by neutrophils (Deshmukh et al., 2020).

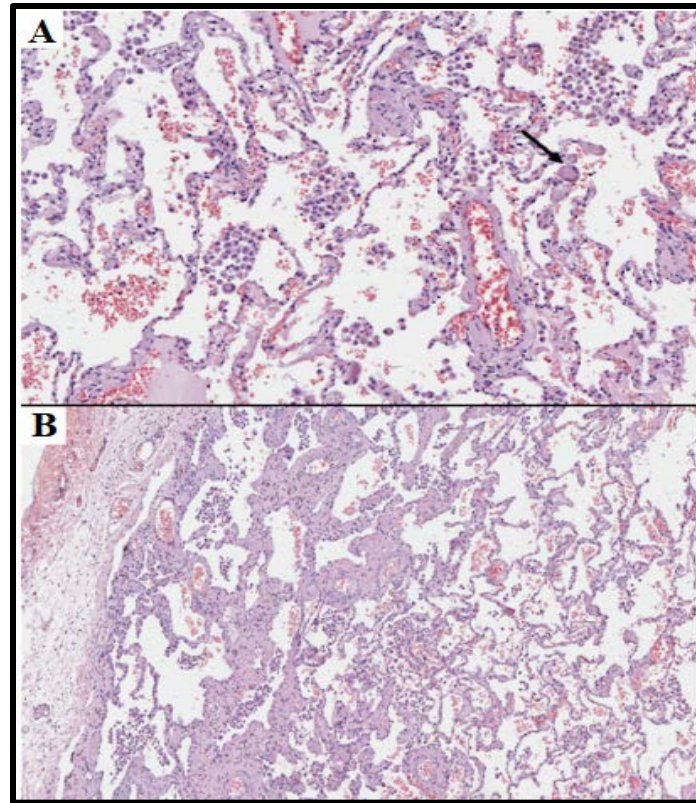


Figure 8:- (A, B) Histological findings of COVID-19 in lungs. (A) Groups of macrophages as well as alveolar hemorrhages and rare giant cells (arrow). (B) The septum of the alveoli presents a slight fibrous thickening restricted to the subpleural region (Pernazza et al., 2020).

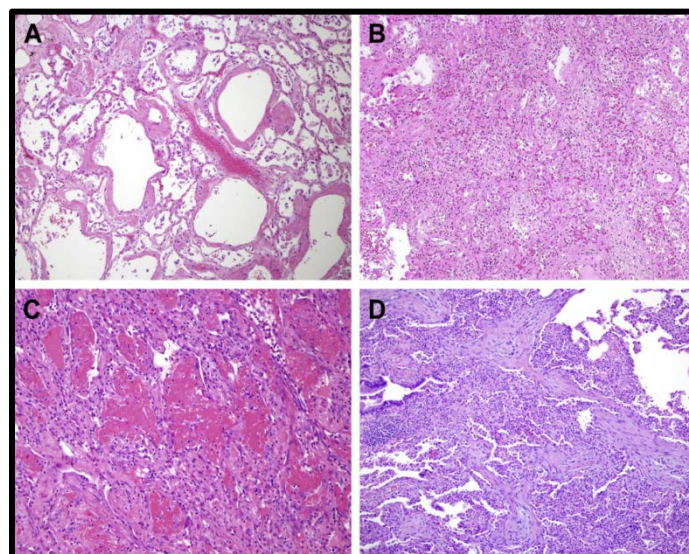


Figure 9:- (A, B, C, D) Histological effects of COVID-19 in terms of diffuse alveolar damage (DAD). (A) Acute exudative phase of diffuse alveolar damage (DAD). (B) Subacute organizing (or proliferative) phase of diffuse

alveolar damage (DAD). (C) Acute fibrinous and organizing pneumonia (AFOP). (D) Organizing pneumonia (OP) (Hariri et al., 2021).

Conclusion:-

The lower respiratory tract starts from the trachea to the paired lungs. It is the main respiratory center of histological and pathological diagnosis. The review is largely focused on the histological effects of COVID-19 on the lower respiratory tract. Diffuse alveolar damage (DAD) remained the principal lung histopathological finding in patients with COVID-19. DAD results from damage of the covering cells of the alveoli and endothelium ending with disarrangement of the blood-air barrier. About the event of pulmonary injury, DAD is classified into three histopathological stages that are acute (exudative), subacute (organizing), and chronic (fibrotic) stage.

Since there is no adequate information about the histological effects of COVID-19 on the lower respiratory system, a perfect understanding of histological changes of the respiratory tract is of great significance especially in the area of pulmonology. Histological changes occurring after COVID-19 are important and may give histologists and pathologists to possess a deep understanding of the respiratory system.

This article may assist internists, pulmonologists, and researchers to understand the effects or histopathological changes of COVID-19 on the lower respiratory system, which may improve the approach of the disease and its prevention. Further data regarding the histological effects of COVID-19 on the lower respiratory tract is needed to adequately define the histopathological changes of the lower respiratory tract associated with COVID-19. Additional comprehensive research concerning histopathological findings is also needed and is important for a comprehensive understanding of the effort to manufacture effective vaccines. Progress done in the area of histology and pathology may help to manage the diagnosis, prevention, and treatment of COVID-19 as well as any similar upcoming diseases.

References:-

1. Alkanlı, N., and Koroglu, P. (2019). HISTOLOGY OF RESPIRATORY SYSTEM AND SURFACTANT PROTEIN D GENE VARIATIONS ASSOCIATED WITH SERUM PROTEIN D LEVELS IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE (1 ed., pp. 41-55). Ankara, Turkey Gece Publishing.
2. Alsaad, K., Arabi, Y., and Hajeer, A. (2020). Spectrum of histopathological findings in coronavirus disease-19, Middle East respiratory syndrome and severe acute respiratory syndrome. *Annals of Thoracic Medicine*, 15(2), 52-53. doi:10.4103/atm.ATM_105_20
3. Brosnahan, S., Jonkman, A., Kugler, M., Munger, J., and Kaufman, D. (2020). COVID-19 and Respiratory System Disorders: Current Knowledge, Future Clinical, and Translational Research Questions. *Arteriosclerosis, Thrombosis, and Vascular Biology*, ATVB AHA120314515. doi:10.1161/ATVB AHA.120.314515
4. Davies, A., and Moores, C. (2010). STRUCTURE OF THE RESPIRATORY SYSTEM, RELATED TO FUNCTION. *The Respiratory System*, 11-28. doi:10.1016/B978-0-7020-3370-4.00002-5
5. Deshmukh, V., Motwani, R., Kumar, A., Kumari, C., and Raza, K. (2020). Histopathological observations in COVID-19: a systematic review. *Journal of Clinical Pathology*, jclinpath-2020-206995. doi:10.1136/jclinpath-2020-206995
6. French, C. A. (2009). Chapter 2 - Respiratory Tract. In E. S. Cibas & B. S. Ducatman (Eds.), *Cytology (Third Edition)* (pp. 65-103). Philadelphia: W.B. Saunders.
7. Hariri, L. P., North, C. M., Shih, A. R., Israel, R. A., Maley, J. H., Villalba, J. A., Mino-Kenudson, M. (2021). Lung Histopathology in Coronavirus Disease 2019 as Compared With Severe Acute Respiratory Syndrome and H1N1 Influenza: A Systematic Review. *Chest*, 159(1), 73-84. doi:<https://doi.org/10.1016/j.chest.2020.09.259>
8. Haschek, W. M., Rousseaux, C. G., and Wallig, M. A. (2010). Chapter 6 - Respiratory System. In W. M. Haschek, C. G. Rousseaux, & M. A. Wallig (Eds.), *Fundamentals of Toxicologic Pathology (Second Edition)* (pp. 93-133). San Diego: Academic Press.
9. Mead, A. (2020). Understanding Coronavirus Disease 2019 (COVID-19): A Mini-review of the present status and future directions. *Life Science Archives*, 6(5), 1937 – 1944. doi:10.22192/lsa.2020.6.5.1
10. Mescher, A. L. (2013). *Junqueira's Basic Histology Text and Atlas* (13 ed.). USA: McGraw-Hill Education.
11. Patwa, A., and Shah, A. (2015). Anatomy and physiology of respiratory system relevant to anaesthesia. *Indian journal of anaesthesia*, 59(9), 533-541. doi:10.4103/0019-5049.165849

12. Pernazza, A., Mancini, M., Rullo, E., Bassi, M., De Giacomo, T., Rocca, C. D., and d'Amati, G. (2020). Early histologic findings of pulmonary SARS-CoV-2 infection detected in a surgical specimen. *Virchows Archiv*, 477(5), 743-748. doi:10.1007/s00428-020-02829-1
13. Rajaa, A., and Nada, M. (2020). IMPACT OF COVID-19 ON HISTOLOGICAL STRUCTURE OF RESPIRATORY SYSTEM. *Life Science Archives*, 6(3), 1855-1859. doi:10.22192/lisa.2020.6.3.4
14. Ross, M. H., and Pawlina, W. (2011). *Histology: A text and atlas: with correlated cell and molecular biology* (6 ed.). Philadelphia: Lippincott Williams & Wilkins, a Wolters Kluwer business.
15. Tamburello, A., Bruno, G., and Marando, M. (2020). COVID-19 and Pulmonary Embolism: Not a Coincidence. *European journal of case reports in internal medicine*, 7, 001692. doi:10.12890/2020_001692