ARDS AND ITS UNDERLYING PATHOGENESIS IN N-COV DISEASE

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ABSTRACT:
ARDS (acute respiratory distress syndrome) and COVID 19 is an alarming concern in the recent n-CoV pandemic. The main pathophysiological events include the severity of hypoxemia and poor respiratory mechanics. The acute respiratory distress syndrome (ARDS) accounts for 40% mortality in about 200,000 critically ill patients annually within the United States including the recent covid pandemic. ARDS is as a result of protein-rich pulmonary edema that causes excessive hypoxemia and impaired carbon dioxide release. The medical disorders related to the development of ARDS consist of sepsis, pneumonia, aspiration of gastric contents, and predominant trauma. The lung injury is caused by pro-inflammatory cytokine release and platelet based damage to the endothelial and epithelial boundaries of the lung. Resolution is delayed due to damage to the lung epithelial barrier, which prevents removal of alveolar edema fluid and deprives the lung of adequate quantities of surfactant. However, there is no effective pharmacological remedy, despite the fact that cell-based total remedy and different therapies currently being tested in scientific trials may additionally provide novel treatments for ARDS. This review thus highlights on the various factors underlying the covid - 19 mediated ARDS.

KEY WORDS: Acute alveolar injury, ARDS-COVID19, Lung compliance, Pathophysiology, VALI.

INTRODUCTION:

ARDS is also referred to as non cardiogenic pulmonary edema, and it is due to acute alveolar injury. Acute alveolar injury is mediated by interleukin 6, TNF alpha and Interleukin 1, which then recruits neutrophils, leading to the damage of the capillary endothelium and accumulation of fluids and protein debris in the interstitial space and alveolar decrease in diffusion of oxygen into the blood (type 1 Respiratory failure). This hypoxia then leads to compensatory pulmonary vasoconstriction, then leads to decrease in lung compliance/ventilation (type3 respiratory failure). Normally the factors preventing the pulmonary edema are increased intravascular oncotic pressure, the interstitial fluid, and the tight junction between the epithelial cells of alveolar sac that prevents the fluid from exudating (*ICU Manual for Nurses* 2017), (Matthay and Zemans 2011).

The corona virus is an acute atypical respiratory disease that emerged from Wuhan, China. The novel coronavirus was named as severe acute respiratory syndrome coronavirus-2 and the seerity varies with the genetic make-up of the individuals (Paramasivam et al. 2020) (SARS-CoV-2, 2019-n CoV). Due to its homology, it causes acute respiratory distress syndrome (ARDS), and high mortality during 2002-2003 (Ksiazek et al. 2003). The outbreak of corona is due to zoonotic transmission with the bats and seafood market in Wuhan city, China, then later it is transmitted from human to human (Li et al. 2020). This virus affects the respiratory system and other organ systems, lower respiratory infection related symptoms

including fever, dry cough and displeasure were reported in the initial case. The incidence and mortality are high in elder population and in incidence is much lower in children. It is now widely recognized that the respiratory symptoms of COVID19 are extremely heterogeneous, ranging from minimal symptoms to significant hypoxia with ARDS (Lu et al. 2020). More therapies are being tested in clinical trials. A large number of countries were implemented to lockdown and social distancing to control the further spread of virus (Girija et al. 2019)**.**

The preliminary idea on this review is to discuss the epidemiology, definitions, and medical disorders related to ARDS, which include the related non pulmonary organ disasters that regularly accompany this syndrome. The second objective is to understand the factors concerning the pathogenesis of lung injury, due to co-infection with other bacterial or resistant fungal strains (Shahana and Muralidharan 2016) that results in the development of acute pulmonary edema. Effective stress in ventilation to lung injury in sufferers with ARDS and also in a dental set-up mediated infections too (Renuka and Muralidharan 2017) is also discussed. This also throws new insights into the mechanisms responsible for the resolution of ARDS, in particular the mechanisms answerable for the clearance of pulmonary edema and the cure for acute lung inflammation. The final goal is to briefly evaluate the current treatment modalities, which are in general targeted on advanced supportive care.

Manifestation of ARDS:

Intense respiratory misery disorder is a dangerous incendiary lung injury shown by hypoxia and firm lungs because of expanded pneumonic vascular penetrability and quite often requiring mechanical ventilation support (Ware 2014), (Monisha, Vishnu Priya, and Gayathri 2019). Respiratory symptoms must have begun within one week of a known clinical insult, or the patient must have new or worsening symptoms (Ashbaugh et al. 1967). On a microscopic level, the disorder is associated with capillary endothelial injury and diffuse alveolar damage. It is characterized by bilateral lung infiltrates and severe progressive hypoxemia in the absence of any evidence of cardiogenic pulmonary edema. ARDS is defined by the patient's oxygen in arterial blood (PaO2) to the fraction of the oxygen in the inspired air (FiO2) (National Heart, Lung, and Blood Institute PETAL Clinical Trials Network et al. 2019). Besides pulmonary infection or aspiration, extra-pulmonary sources include sepsis, trauma, massive transfusion, drowning, drug overdose, fat embolism, inhalation of toxic fumes, and pancreatitis. These extra-thoracic illnesses and/or injuries trigger an inflammatory cascade culminating in pulmonary injury (Combes et al. 2018). Some risk factors for ARDS include:Advanced age, Female gender, Smoking, Alcohol use, Aortic vascular surgery, Cardiovascular surgery, Traumatic brain injury. There are numerous clinical disorders associated with the development of ARDS, consisting of sepsis, pneumonia, aspiration of gastric contents, and principal trauma . The pathology of ARDS in the lung was first described in 1977 by using Bachofen & Weibel in a seminal publication. Since the early medical and pathologic descriptions of ARDS, large primary and scientific studies have been devoted to knowledge of epidemiology, pathogenesis, and determinants of scientific consequences in ARDS. Also, numerous medical trials have been carried out to test new treatments for ARDS (Ashwin and Muralidharan 2015).

Immunopathology behind ARDS:

ARDS causes diffused alveolar damage in the lung, there is hyaline membrane formation in the alveoli, acute stage is followed by interstitium widening by edema followed by fibroblast proliferation. COVID19 ARDS causes the typical ARDS pathological charges of diffuse alveolar damage in lungs. Entry of SARS-CoV 2 is mediated by viral spike glycoprotein, virus hold of host cell machinery employing the use of viral main protease 3CL pro and NSP15 endonuclease. Pulmonary thrombosis is a common sepsis which is induced in ARDS. In fatal cases, there is diffuse micro vascular thrombosis, suggesting a thrombotic microangiopathy, and most deaths from COVID 19 ARDS have evidence of thrombocytes DIC.

Alveolar macrophages residing within the air spaces and interstitium are the earliest immune-cell to check the presence of pathogenesis or cell injury (Iwasaki, Foxman, and Molony 2017). In opposite, the denitrify cells acts as an interface between the innate and adaptive immune system and resides deep to the airway epithelial layer within interstitium, the antigen presenting cells will mature and migrate to the lymph nodes to prime the adaptive responses when exposed to presentable antigen (Worbs, Hammerschmidt, and Förster 2017). Several cytokines are involved, the wave of cytokines attracted towards the circulating neutrophils and monocytes stimulates AECs to increase the production of antimicrobial peptides and chemokines, and to enhance phagocytosis.

SPECIFIC FEATURES OF COVID19 RELATED ARDS:

Injury site of COVID 19:

ARDS occurs because of an acute systemic inflammatory response, which can be due to insults to the lung, either direct or indirect. The early exudative stage affords diffuse alveolar damage with destruction of epithelial and endothelial cells. COVID-19 specifically affected the breathing system with minor harm to other organs. Studies suggested that acute myocardial damage (7.2–17%) and acute renal harm (2.9–15%) could occur in severe patients. The stated prevalence of ARDS becomes 15.6–31%, higher than that of different organ injuries. The most common respiration symptom of COVID-19 is dry cough (59.4–82%). Sputum production was less that cannot be cured even with alternative medications using natural medicines (Marickar, Geetha, and Neelakantan 2014). It cautioned that injury to the alveolar epithelial cells was the main motive of COVID-19-associated ARDS, and endothelial cells were less damaged with therefore much less exudation. Endothelial cells line the internal floor of blood vessels in all organs. It changed into feasible because of much less harm to the endothelial cells, different organ functions were much less concerned in COVID-19 patients.

Specificity of clinical features:

The respiratory system was mainly worried in COVID-19 sufferers as stated above. Some sufferers had a low oxygenation index, indicating severe respiratory failure. Chest imaging findings suggested the involvement of each lung. Chest computed tomography (CT) scans usually showed multifocal bilateral patchy shadows and/or ground-glass opacities; a few patients showed a mixed pattern of ground-glass opacities and consolidation. The CT effects indicated diffuse and extreme lung injury. However, the clinical manifestations have been quite moderate in some patients as seen in some infections initiated by drug resistant bacteria (Girija As and Priyadharsini J 2019). These patients might have no complaint of dyspnea, no large growth in respiratory rate, and no breathing distress. Hemodynamics and indexes of tissue perfusion together with lactate were also fairly stable. The scientific signs and symptoms were inconsistent with the severity of laboratory and imaging findings. However, these sufferers may additionally become worse unexpectedly and want to be monitored closely. Blood carbon dioxide levels may be a meaningful indicator for invasive mechanical ventilation.

Ventilator associated lung injury:

Mechanical ventilation is fundamental on the side of patients with respiratory distress who are basically sick. Nonetheless the utilization of this method has friendly impacts, including expanded danger of pneumonia, weakened cardiovascular execution and troubles related with sedation and loss of motion. ACT Is an instrument where secretion mobilization and expectoration and to moderate difficulties in discharge maintenance. It controls lung volume, gas stream, pneumonic weight, and compression strength (K et al. 2018). In addition the strain to the lung regardless whether plus or minus, can cause harm known as Ventilator associated lung injury (VALI)(Girija et al. 2019). In spite of troubles in recognizing the impacts of mechanical ventilation from those of basic issue, VALI significantly helps patients with the

most extreme type of lung injury, intense respiratory misery disorder, in addition to change of mechanical ventilation,VALI is kept to a base that improves endurance of patients with ARDS (Vallbracht, Schmidt, and Hoetzel 2009). A dialogue of the pathogenesis of ARDS is not complete without an exam of the contribution of fine strain air flow to the lung injury.

The multicenter ARDS Network trial of 861 patients verified a marked reduction in mortality and in severity of lung injury with a lung-defensive ventilatory strategy, and it supplied convincing proof that formerly regularly occurring ventilatory strategies using excessive tidal volumes and high airway pressures amplified lung harm in patients with ARDS. Subsequently, animal research discovered that a ventilation approach with lower tidal volumes and lower airway pressures is shielding in ALI due to numerous mechanisms, consisting of reduced lung endothelial injury, reduced lung epithelial damage, reduced lung inflammation, and accelerated resolution of alveolar edema. Thus, ventilation with better tidal volumes and elevated airway pressures causes greater lung infection and likely effects in direct mechanical injury to the lung epithelium and endothelium as well. Follow-up human research (Smiline, Vijayashree, and Paramasivam 2018) have established that patients who're ventilated with decrease tidal volumes and lower airway pressures had a reduction both (a) in plasma degrees of interleukin (IL)-8, IL-6, and soluble TNF receptor 1, and (b) in the number of neutrophils and inflammatory markers inside the air spaces of the lung . Furthermore, levels of the alveolar epithelial type II cellular marker SP-D and the receptor for superior glycation stop products (RAGE) had been also reduced in sufferers who were ventilated with a lower tidal extent. Interestingly, improved plasma RAGE stages identified those sufferers who are maximum possibly to gain from a lower–tidal volume approach. Thus, unfavorable ventilatory strategies compound the degree of lung injury in patients with ALI/ARDS through a whole lot of mechanisms.

Respiratory system compliance:

COVID-19 reportedly has four stages: a pre-symptomatic phase of fever, cough, and generalized malaise heralded by high viral loads eventually differing based on their genetic make-up (Priyadharsini et al. 2018) in severely affected cases. After about a week, the second stage manifests with viral pneumonia that involves the lower respiratory tract (while viral loads in the upper respiratory tract decrease exponentially)(Pratha, Ashwatha Pratha, and Geetha 2017). A vast majority of patients show clinical improvement as protective humoral responses are developed at this stage of the disease. A minor proportion of individuals progress to the third phase of CoVID-19 by developing symptoms of hypercytokinemia which is characterized by exaggerated levels of pro-inflammatory cytokines and other pathognomonic biomarkers of inflammation, leading to the rapid onset of acute respiratory distress syndrome (ARDS) and multi-organ failure (Stage 4). It is also intriguing to know that many individuals with COVID-19 have not developed ARDS (Maajida Aafreen, Rv, and Thangavelu 2019). The median time from development of symptomatic disease to death from COVID-19 is ~2–8 weeks due to magnified cytokine storm (Girija, Shankar, and Larsson 2020).

Not all the instances of increased respiratory disappointment brought about by COVID19, were ARDS. The average CT discovery of COVID19 indicated respective ground glass shadow with fringe lung circulation (Lyons and Callaghan 2020). In fact there was solidification and exudation, it was an ordinary ARDS picture that can vary in case of co-infections with any kind of drug resistant bacteria (Vijayashree Priyadharsini, Smiline Girija, and Paramasivam 2018). ARDS is a condition related to numerous malady forms, bringing about decreased lung consistency and serious hypoxemia (Scholten et al. 2017). Lung consistency may be ordinary in some patients who met ARDS. There was obviously inconsistent with

ARDS caused by other factors. In addition the lung compliance was relatively high in some COVID19 related ARDS patients, which was inconsistent with severity of hypoxemia.

Management protocols:

In common place ARDS, non stop neuromuscular blocking operators, high portion corticosteroids and enlistment moves were the most much of time utilized adjunctive treatments. In COVID19 ARDS the proof of fundamental steroids is still rare and just suggested in patients with corresponding stun which has been lethargic to vasopressors. There are worries that steroids may increment viral shedding and perhaps lead to viral shedding and that leads to higher death rates and may not be cured upon natural medications too (Vaishali and Geetha 2018) Chymotrypsin like protease is a target in design of potential anti coronavirus inhibitor, research by TCS says that; in India 31 modules out of 160,0000 have been identified as most effective protease inhibitor against COVID19 (Sengupta n.d.). The mortality rate comparison between the ARDS and the ARDS COVID19 patients, is 44% higher in COVID19 and ARDS. Currently various immuno-modulators and pro-inflammatory blockers are implemented to the magnified cytokine storms

Hypoxic breathing failure in ARDS normally results from intrapulmonary ventilation-perfusion mismatch or shunt and usually calls for mechanical ventilation. Compared to standard oxygen therapy, high-glide nasal oxygen (HFNO) reduces the need for endotracheal intubation for the patients with ARDS. WHO recommended that HFNO should be utilized in selected patients with hypoxic respiratory failure. Studies indicated that HFNO is more suitable for sufferers with mild ARDS(Pratha, Ashwatha Pratha, and Geetha 2017). However, in keeping with clinical situations, HFNO may be secure in both mild and slight-slight COVID-related ARDS sufferers, or even some mild-extreme sufferers. Some sufferers with an oxygenation index of 100 mmHg can remain fairly solid with the help of high-glide nasal oxygen (HFNO), however depends on individuals genetic make-up to tolerate (Paramasivam, Vijayashree Priyadharsini, and Raghunandhakumar 2020). This is absolutely inconsistent with the stratified remedy strategies of ARDS due to other factors associated with other pathogenic microbes (Girija, Jayaseelan, and Arumugam 2018).

CONCLUSION:

Albeit, numerous factors associated with the improvement of ARDS, the pathogenesis of covid ARDS, entails inflammatory damage to the lung endothelium and epithelium, leading to edematous fluid into the air spaces. Limited medical resources, limited sample size, single centered designs further results in poor understanding of the immunopathogenic mechanisms underlying covid associated ARDS. This review had thus highlighted the various factors related to the development of ARDS in covid patients leading to exorbitant mortality rate. However, we emphasize more clinical and experimental studies related to the same to be undertaken in order to acquire an intimate knowledge on ARDS paving the way to a successful survival rate among covid patients.

AUTHOR CONTRIBUTION:

N.Padma priyaa:

1. Execution of work
2. Data collection
3. Drafting of manuscript

Smiline Girija AS

1. Concept and Design of the study
2. Validation of the data collection

3. Revision and proofreading of the review

CONFLICT OF INTEREST:
None to declare

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