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ASIF AHMAD

SU91-MSAHW-F23-021

FAHS

Lung Protective Ventilation Strategies for Acute Respiratory Distress Syndrome (ARDS) Patients in ICU



SUPERIOR UNIVERSITY

Thesis Submitted to

The Superior University Lahore

In Partial Fulfillment of the

Requirement for the Degree of

Master of Science in Allied Health Sciences

By

Asif Ahmad

Roll No. SU91-MSAHW-F23-021

Session: 2023-2025

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Associate Professor

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Asif Ahmad :

Signature: _____

Examination Committee:

Session Chair:

Signature: _____

a) External Examiner:

Signature: _____

b) Internal Examiner:

Signature: _____

c) Supervisor Name: Dr. Usra Naeem

Signature: _____

d) PL/HOD: Dr. Hafiz Shehzad

Signature: _____

e) Dean: Prof. Dr. M. Naveed Babur

Signature: _____

f) Controller of Examination: Dr. M. Haris

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DEDICATION

This work is dedicated to my beloved parents, whose unwavering guidance, support, and assistance have been instrumental in the completion of my MS Allied Health Sciences Degree. Their constant prayers and encouragement have been the cornerstone of my success. Without their help, I would not have been able to achieve this significant milestone.

I am profoundly grateful to Allah Almighty for blessing me with such loving and caring parents. Their sacrifices, wisdom, and faith have been my guiding light throughout this journey. This accomplishment is as much theirs as it is mine, and I am forever indebted to them for their enduring love and support.

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LIST OF ABBREVIATIONS

ARDS	Acute Respiratory Distress Syndrome
ICU	Intensive Care Unit
AECCs	Atrial Ectopic Beats
VILI	Ventilator-Induced Lung Injury
HFOV	High Frequency Oscillatory Ventilation
ECCO2R	Extra Corporeal Carbon Dioxide Removal
VFDs	Ventilator Free Days
RCT	Randomized Control Trials
PaO ₂	Partial Pressure Of Oxygen
FiO ₂	Fraction Of Inspired Oxygen
PEEP	Positive End Expiratory Pressure
CPAP	Continue Positive Airway Pressure
V/Q	Ventilation Perfusion
ECMO	Extra Corporeal Membrane Oxygenation
VVECMO	Veno-Venous Extra Corporeal Membrane Oxygenation
VAECMO	Venoarterial Extra Corporeal Membrane Oxygenation
FACTT	Foundation For Accountability

ABSTRACT

Acute Respiratory Distress Syndrome (ARDS) is a severe respiratory failure characterized by extensive destruction of the air sacs, inefficient oxygenation, and a mortality rate of approximately 30-40%. The primary supportive treatment is mechanical ventilation, although when not applied properly, it may lead to ventilator-induced lung injury (VILI), which could deteriorate the patient. To minimize this risk, Lung-Protective Ventilation (LPV) measures are applied to minimize lung damage and yet ensure appropriate oxygen and carbon dioxide levels. The present research assesses the effectiveness of LPV techniques in ARDS patients who are admitted to the Intensive Care Unit (ICU).

The main objective of the study was to determine the impact of the LPV methods, including maintaining a plateau pressure of less than 30 cmH₂O, the application of the appropriate Positive End-Expiratory Pressure (PEEP), and the application of low tidal volumes (less than 6 mL/kg of predicted body weight) on patient outcomes. The secondary objective was to study the impact of other interventions, such as recruitment maneuvers, permissive hypercapnia, and prone positioning, on the reduction of the severity of illness and mortality. It was a cross-sectional study of 139 ARDS patients diagnosed according to the Berlin criteria. Out of them, 79 (56.8) patients were given LPV, and 60 (43.2) patients were given conventional ventilation with higher tidal volumes. Ventilation settings, tidal volume, PEEP, FiO₂, and P/F ratio, and clinical outcomes (mortality rate, length of stay in ICU, ventilator-free days (VFDs)) were recorded. The correlation between ventilation strategies and patient outcomes was investigated statistically.

The mean PaO₂/FiO₂ ratio was 153.69, and most of the patients were categorized as moderate ARDS. Patients treated using LPV had better outcomes, such as increased ventilator-free days, shorter ICU stays (average 12.4 days), and shorter hospital stays (average 15.6 days) than those treated using conventional ventilation. The mortality rate was a bit lower in the LPV (28.4) compared to the conventional (32.3), but the difference was not significant. Optimized PEEP and prone positioning were observed to improve oxygenation, especially in patients with severe ARDS (P/F < 150 mmHg).

CHAPTER 1

INTRODUCTION

1.1 ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS)

Although Acute Respiratory Distress Syndrome (ARDS) was first described almost 50 years ago, it has continued to be a significant cause of morbidity and mortality on a global scale. Approximately 3 million individuals are infected by this condition each year. In intensive care units (ICUs), ARDS is the cause of about 10% of patient hospitalization, and individuals diagnosed with it have a high mortality rate of almost 40% [1] [2] . ARDS is clinical manifestation of complex medical disorders characterized by grossly compromised gas exchanges and acute respiratory failure. The epidemiological evidence of the syndrome in 50 countries of the world indicates that many clinicians do not fully comprehend the syndrome; thus, close to 40 percent of patients are diagnosed late or not diagnosed at all [1, 3]. A Due to the high diversity of the patient population, the medical community is shifting towards a one-size-fits-all approach. Rather, clinicians are working on finding treatable characteristics-specific biological or clinical features of subsets of patients. It is an important move towards the successful use of precision medicine in critical care. [4]. The natural heterogeneity of the ARDS group has triggered a paradigm shift to finding treatable traits, a shift that is necessary to introduce meaningful use of precision medicine in intensive care. The recent evidence is more in favor of the presence of specific hyper-inflammatory and hypo-inflammatory sub-phenotypes, therefore one-size-fits-all approach high efficacy in therapeutic clinical trials.

1.2 The Development of the ARDS Definition

Acute Respiratory Distress Syndrome (ARDS) in critically ill patients was initially reported in a 1967 study of 12 cases. The report associated ARDS with such conditions as sepsis and pneumonia and described the main clinical and pathological features, including decreased lung compliance, increased effort during breathing, low oxygen in the blood (hypoxemia), pulmonary edema without cardiac issues (non-cardiogenic pulmonary edema), and the necessity of positive pressure ventilation [5].

1.3 Precipitating disorder

1.3.1 Conventional ARDS causes

Acute Respiratory Distress Syndrome (ARDS) may occur due to numerous causes, both infectious and non-infectious. These stimuli can cause direct lung damage by local inflammation or indirect damage by the circulation of pro-inflammatory and harmful substances in the blood. The most widespread cause of ARDS is sepsis. In addition to non-pulmonary sepsis, lung infections such as pneumonia are also major contributors. Ordinary non-infectious causes are severe shock due to trauma, stomach content aspiration, pancreatitis, and repeated blood transfusions. Even though they are not direct causes, some factors, such as alcohol consumption, air pollution, and cigarette smoking, have the potential to increase the risk of developing ARDS in individuals with underlying conditions. Transfusion-related acute lung injury can also be triggered by a combination of blood transfusion with other triggers. Genetic variation can also contribute, but most of them are uncommon and only cause a minor risk increment.[12]

1.3.1.1 Pathophysiology

Acute respiratory distress syndrome (ARDS) is a complicated medical condition with a limited scholarly understanding of its exact pathophysiological mechanism despite comprehensive work in recent decades. One major reason for this gap is that animal models do not fully represent how the disease behaves in humans. In addition, it is very challenging to carry out detailed mechanistic research in patients who are critically ill, especially during the acute phase of the disease. These limitations are hindering progressive research on the development and progression of acute respiratory distress syndrome [13]. One of the main reasons ARDS develops is the activation and imbalance of several interconnected damage response pathways in the lungs as well as in the whole body. The inflammatory pathways are one of the major pathways against ARDS. The inflammation, coupled with coagulation processes, plays an important role in protecting the body against infection or injury. Under normal conditions, they help the body heal and recover. However, when these responses become excessive or uncontrolled, they can cause more harm than benefit, leading to lung injury and worsening of the patient's condition.

1.3.1.2 Harm to the lung's endothelial and epithelial barriers

Only a thin basement membrane separates the thin capillary and alveolar epithelial cell layers endothelium that comprises the alveolar capillary barrier, facilitating simpler gas exchange. Alveolar–capillary barrier damage to both layers is the direct cause of the ARDS's characteristic physiological abnormalities.[13] The lung epithelium is composed of a thick layer of flat alveolar

epithelial type I cells interspersed with alveolar epithelial type II cells. The extent of lung epithelial damage is one significant determinant affecting survival in ARDS patients.[14] In ARDS, the extent of lung epithelial injury can differ. Damage can manifest in a variety of ways, including frank epithelial cell necrosis with alveolar basement membrane denuding, slight increases in paracellular permeability caused by intercellular junction damage, or epithelial activation with adhesion molecule expression and pro-inflammatory and pro-coagulant pathway activation. Alveolar flooding and reduced fluid transport by the alveolar epithelium—the body's natural defensive mechanism for preserving a dry airspace—are caused by damage to the tight lung epithelial barrier.[15] Type II cell damage may reduce the generation of surfactant; [16] alveolar flooding may also deactivate surfactant.[17] Necrosis of the lung epithelial cells causes intracellular contents to seep into the airspace, releasing disease-associated molecular patterns that can intensify pro-inflammatory signaling. [18]

1.3.1.3 Physiological repercussions of alveolar–capillary barrier damage

Acute injury in ARDS causes the destruction of endothelial and epithelial barriers of the lung, which causes gas exchange difficulties, increased breathing effort, and visible changes on chest diagrams. When these barriers start to be more permeable, the protein-rich fluid starts to leak out of the blood vessels into the air spaces and fills the alveoli. Meanwhile, the usual mechanism of clearing the fluid in the alveoli is impaired. This system tends to push surplus fluid into the surrounding tissue, where it is taken into the blood and eliminated through the lymphatic system. Failure of this process leads to further accumulation of fluid, which results in intense flooding of the alveoli. [19]

1.4 Lung and systemic Inflammation

One of the main characteristics of ARDS that harms the endothelium and epithelium of the lungs is acute inflammation, both in the body and in the lungs. In normal airspaces, neutrophils are not common. Nevertheless, during the initial phases of acute respiratory distress syndrome (ARDS), such cells secrete substances into the airways, including proteases, reactive oxygen species, and pro-inflammatory lipid mediators, such as prostaglandins and leukotrienes. The extracellular traps of neutrophils in this disease process consist of DNA, histones, and proteases. These traps may also enhance inflammation by stimulating the NLRP3 inflammasome, which causes the release of interleukin-18 and interleukin-1 β locally. Most of the recruitment of neutrophils is controlled by both resident tissue cells and recruited macrophages. [22] Macrophage pattern recognition receptors attach to molecular patterns associated with pathogens or diseases, causing macrophages to exhibit

a proinflammatory phenotype. Proinflammatory cytokines and neutrophil chemo attractants including interleukin-8 are then released as a result. Neutrophil chemo attractants can also be released by lung epithelial cells.[23] The capillary wall is the main route by which neutrophils enter the lung in response to chemoattractant gradients. Then, they appear to be under the control of interstitial fibroblasts as they travel adjacent to between endothelium cells and alveolar epithelial cells.[20] Transcytosis, however, has also been noted. There is currently evidence that intra-alveolar inflammation in ARDS is regulated by networks of cytokines and a range of safe cells, including dendritic cells, lymphocyte subsets, and macrophages [24].[25]. In addition to lung inflammation, patients with ARDS often have systemic inflammation, which probably contributes to the high rate of non-pulmonary organ failure in ARDS. Non-pulmonary organ failure may also result from relationships between the kidneys and other organs, such as the brain and the lung [26][27]. Poor short- and long-term results for ARDS are linked to both kidney and brain damage.[28]

1.5 DIAGNOSIS

Even though the Berlin definition of ARDS has certain limitations compared to the AECC criteria, the four primary clinical characteristics required to diagnose the condition are similar in both. These are the degrees of hypoxemia, the non-hydrostatic etiology of pulmonary edema, the interval between the precipitating event and the development of respiratory failure, and the results of chest radiographs. Nonetheless, determining the relationship between the onset of respiratory failure and the precipitating event is a matter of physician discretion, which may occasionally result in the underdiagnosis or undertreatment of ARDS. To be more specific, the Berlin definition states that bilateral opacities on the chest radiographs should be associated with pulmonary edema and cannot be entirely attributed to other diseases like masses, nodules, effusions, or lung collapse. A series of reference chest radiographs was also given to assist in diagnosis by demonstrating results that could be either consistent, inconsistent, or unclear in ARDS. Although there are more explicit guidelines and the presence of example images, interobserver agreement in the interpretation of the chest radiographs is not optimal and does not increase significantly even with formal training. [30] Whether bilateral infiltrates—that is if they are connected to a pathogenic process in order to develop ARDS or a reaction to certain therapies should continue to be a crucial part of the syndrome's description should be considered in future revisions to the diagnosis of ARDS. If not, considering eliminating this criterion from ARDS classifications in the future or using alternative modalities in its place (such computed tomography or lung ultrasonography) if further study shows that they are more accurate. It's interesting to note that additional physiological measurements (like

respiratory system agreement [Cr_s] ≤ 40 mL/cm H₂O and corrected minute drying ≥ 10 L/min), which have previously been associated with worse outcomes and higher ARDS severity, did not improve The ability of severe ARDS to forecast. It would be very helpful to find a biomarker that improved the sensitivity and specificity for diagnosing ARDS or organizing its severity.[31] Despite extensive study in this field, no biomarker is yet sufficiently informative to be incorporated into an ARDS definition. More precise and uncomplicated methods are needed to measure extravascular lung water and respiratory vascular penetrability

.

1.6 Major Studies and Advances in Therapy

There are limited treatment options available for Acute Respiratory Distress Syndrome (ARDS), however medically advance to support live in critical situations. Mechanical ventilation remains the cornerstone of management, mainly aimed at minimizing ventilator-induced lung injury (VILI) [32]. VILI is a type of iatrogenic lung damage that is a potential factor to aggravate the patient's condition and lead to progressive multi-organ failure or even death. It can also intensify the systemic inflammatory response, making the clinical picture more complicated. Based on physiological targets for adequate gas exchange, the usual therapeutic approach in ARDS begins with lung-protective ventilation strategies and may gradually move toward more invasive supportive measures if required [33]. The overall management plan is further dependent on multiple factors, i.e., the patient's clinical status, the underlying cause of ARDS, and the facilities available at the treatment center, as well as an effective approach to rehabilitating the patients. In recent years, several important developments have been explored as potential treatment options, i.e., lung recruitment maneuvers, high-frequency oscillatory ventilation (HFOV), use of statins, extracorporeal carbon dioxide removal (ECCO₂R), and prone positioning. The advanced modalities are under consistent scholarly evaluation to improve the efficacy of ARDS treatment.

1.7 Prevention

Prevention is essential since ARDS is characterized by high morbidity and mortality rates. Platelets can potentially contribute to the pathogenesis and healing of lung injury and hence are a potential therapeutic target. This concept is supported by observational studies that antiplatelet therapy, including aspirin, may be used to prevent ARDS in patients at high risk. To investigate this, a multicenter randomized controlled trial (RCT) was carried out on patients at high risk of ARDS, i.e., with a lung injury prediction score of 4 or above. In this research, the eligible patients were randomly allocated within 24 hours of their arrival at the emergency department to either 81 mg of aspirin or a placebo daily throughout their stay in the hospital until discharge or death. The

primary result did not reveal any significant difference in the incidence of ARDS between the two groups (odds ratio [OR], 1.24 [95% CI, 0.672.31]). Also, secondary outcomes and adverse events, such as hospital stay length, 28-day survival, 1-year survival, and ventilator-free days, did not show any significant differences. These findings do not favor the use of aspirin in the prevention of ARDS in patients at risk.

1.8 Supplemental Treatments: Lung-protective ventilation is not necessarily sufficient to prevent the worsening of ventilator-induced lung injury (VILI). Further reduction of VILI can be used to achieve better patient outcomes by using lower tidal volumes. Nevertheless, the development of respiratory acidosis and hypercapnia may limit this approach. To control this, it is possible to resort to extracorporeal carbon dioxide removal (ECCO2R), in which case an external device assists in the removal of CO₂ in the blood [40] By decreasing the amount of ventilatory support, especially tidal volume, it is possible to implement an ultraprotective ventilation strategy, i.e., ventilation using even lower tidal volumes than the recommended care. The method reduces lung damage through decreased tidal volume; minimal alveolar carbon dioxide is removed from the lungs to reduce mechanical load [41]. This was tested in a small randomized controlled trial comparing extracorporeal carbon dioxide removal (ECCO2R) with very low tidal volumes of 3 mL/kg predicted body weight to the traditional lung-protective approach of 6 mL/kg predicted body weight. The main outcome, which was the ventilator-free days at day 28 and day 60, did not exhibit a statistically significant difference between the two groups [42] Nevertheless, in a post hoc study of patients with a PaO₂/FiO₂ ratio of 150 mmHg or less, the ventilator-free days were significantly greater in the ECCO2R group than in controls at day 28 and day 60. According to a recent systematic review, ECCO2R is still to be regarded as an experimental treatment. Current trials, such as the Research on Extracorporeal Support for ARDS (REST) and the SUPERNOVA trial, are likely to give additional evidence on its efficacy when used in conjunction with protective ventilation measures. Because ECCO2R is an invasive intervention, the choice of appropriate patients is a significant issue. A precision medicine approach can assist in this respect. According to recent physiological research, patient selection can be guided by parameters like compliance of the respiratory system and pulmonary dead space [42] The compliance respiratory system (C_{rs}) is obtained by dividing tidal volume (V_T) by the difference between the plateau pressure (P_{plat}) and end-inspiratory pressure (PEEP). The ability to identify patients with certain physiological profiles can enhance ECCO2R outcomes. Moreover, prone positioning is useful in the prevention of ventilator-induced lung injury. Mechanical stress is more evenly distributed throughout the lungs when patients are put in the prone position, resulting in more uniform lung inflation and possibly

less additional damage [43] Many clinical trials have advanced in sophistication over the last 20 years (e.g., using longer periods of prone positioning and increasingly aiming patients with more unadorned ARDS).[44] resulted in a major multicenter RCT showing that 90-day mortality was significantly decreased by putting ARDS patients in the disposed to position for the minimum 16 hours per day if their PaO₂/FIO₂ ratio was 150 mm Hg or less (hazard ratio [HR], 0.44 [95% CI, 0.29-0.67]).[45] There were no changes in the adverse effects across the groups, with the exception of a significantly higher occurrence of cardiac arrests in the supine group (31 versus 16 in the prone group; P =.02). It is advised that institutions wishing to implement this technique become proficient in prone posture if they want to observe results similar to those in the RCT, given the high level of prone positioning experience among the centers participated in this study.[46, 47]

1.9 Pharmacologic Therapies

Alveolar flooding and development of pulmonary edema are two significant pathophysiologic characteristics observed in acute respiratory distress syndrome patients. Experimental data suggests that 2-agonists are potentially effective in clearing up pulmonary edema by activating 2 receptors on alveolar type I and type II cells. When these receptors are activated, salt and fluid transport across the alveolar membrane is enhanced, and this hastens clearance of excess lung fluid. This hypothesis was tested in a single-center, phase II randomized controlled trial, in which a continuous 7-day salbutamol infusion was linked to a significant decrease in extravascular lung water, indicating a potential therapeutic use of 2-agonists in the treatment of pulmonary edema in ARDS [49]

1.10 MANAGEMENT OF ARDS

1.10.1 MECHANICAL VENTILATION

Acute respiratory distress syndrome (ARDS) is a complicated disorder where various alveoli act in different ways when ventilating. [50]. There are also collapsed alveoli that are not involved in the exchange of gases, ones that open and close each time an individual breathes, and others that become overdistended and damaged [37]. Consequently, the fraction of the lung that literally participates in ventilation is significantly decreased. This is a smaller and functional segment of the lung, which is often known as the baby lung. The primary causes of ventilator-induced lung injury (VILI) are repetitive collapse and reopening of already damaged alveolar units, and overdistension of the already limited functional baby lung during tidal ventilation. [51] There are two crucial principles in the lung-protective ventilation strategies applied in the management of ARDS. The initial one is low tidal volumes that are used to avoid overdistension and additional damage to functional lung units. The second is the use of sufficient positive end-expiratory pressure (PEEP),

which is used to reduce cyclic atelectasis and enhance oxygenation by maintaining alveoli open at end-expiration. In addition to these fundamental strategies, other areas of mechanical ventilation were also investigated in clinical studies, such as the various ventilation modes, recruitment maneuvers, and the comparison of high versus low PEEP in patients with ARDS [52, 53, 54, 55, 56].

1.10.2 Lung Protective Ventilation

The use of lung-protective ventilation is believed to be critical in the treatment of ARDS. The ARDS Net Trial, published in 2000, provided the best evidence in support of low tidal volume ventilation. In this massive randomized controlled trial involving 861 patients, patients ventilated with lower tidal volumes, with a mean of 6.2 ± 0.8 mL/kg of predicted body weight, had much lower mortality rates than patients ventilated with conventional high tidal volumes of 11.8 ± 0.8 mL/kg (31% vs. 39.8%, $p = 0.007$) [58]. Mean plateau pressures also differed significantly between the protective (25 ± 6 cmH₂O) and conventional (33 ± 8 cmH₂O) groups. Moreover, a meta-analysis of six randomized controlled trials of 1297 ARDS patients showed that ventilation with tidal volumes of 7 mL/kg or less was associated with a significant reduction in 28-day mortality relative to ventilation with tidal volumes of 10-15 mL/kg (27.3% vs. 36.9%). The plateau pressure of 31 cmH₂O or less in the control groups did not reduce mortality on its own [59]. Low tidal volume ventilation is associated with a typical outcome of hypercapnia owing to decreased minute ventilation. To maintain the lung-protective measures without raising the ventilator injury, the idea of permissive hypercapnia permits the increase of the carbon dioxide level in the arteries above the normal range. Nevertheless, there is no definite low pH limit or entirely safe high CO₂ concentration. The majority of clinicians suggest the persistence of protective ventilation and the correction of severe metabolic acidosis with sodium bicarbonate in case of a pH lower than 7.2. The other technique that is being studied is extracorporeal carbon dioxide removal (ECCO₂R), also referred to as ultraprotective ventilation, which allows the further decrease of tidal volumes to almost 3 mL/kg of predicted body weight [41, 60]. Even though ECCO₂R has the potential to mitigate the ventilator-induced lung injury compared to conventional protective ventilation, comparative studies with other ventilatory approaches like bicarbonate therapy are still scarce, and its general effect on ARDS outcomes is yet to be seen. To conclude, tidal volumes of 4-8 mL/kg based on body weight and plateau pressure kept at less than 30 cmH₂O are highly encouraged as lung-protective ventilation in all patients with ARDS.

1.10.3 Positive End Expiratory Pressure

Positive end-expiratory pressure (PEEP) is significant in the prevention of atelectrauma in

patients with acute respiratory distress syndrome (ARDS). As it has been mentioned above, low tidal volumes are considered one of the two key elements of lung-protective ventilation to prevent tidal overdistension. The second important factor is the use of the right PEEP. PEEP enhances oxygenation and decreases mechanical stress and strain on damaged lung tissue by stimulating the recruitment of alveoli and inhibiting the recurrent collapse of unstable lung units. End-expiration maintenance of alveoli openness prevents functional lung volume and minimizes cyclic damage [51]. Nonetheless, there are possible complications of PEEP. High concentrations can cause a rise in intrapulmonary shunts, physiological dead space, and pulmonary vascular resistance. There is also the possibility of overdistension of already open alveoli, which causes further lung damage. Although there has been a lot of research, no universally agreed-upon definition on what constitutes higher or lower PEEP. The majority of clinical trials have compared lower PEEP and higher inspired oxygen concentrations (FiO_2) with higher PEEP and lower FiO_2 levels. The ARDSNet group significantly embraced this approach in their pioneering ventilation studies [62, 63].

1.10.4 Recruitment Maneuvers

A enrollment technique is a flue interference that improves oxygenation and volume distribution by temporarily raising airway pressure, opening the compressed alveoli.[64] The most popular approaches in numerous research include incremental PEEP/staircase/stepwise and sustained inflation/traditional, even if there are various ways to carry out the hiring process recruiting maneuver.[60, 65] The ventilator must be put in CPAP mode and pressures between 35 and 50 cmH₂O must be utilized for 20 to 40 seconds in order to produce sustained inflation. The pressure support needs to be adjust to zero in order to stop extra pressure increases.[66] PEEP is gradually raised every two to three minutes while Plateau pressure PEEP, or driving pressure, is constant when using a staircase or incremental PEEP approach. Following that, PEEP is gradually decreased to the ideal PEEP level, which is established by agreement and oxygenation.[54, 66] It is recommended to closely Observe the patient for hemodynamic instability and hypoxia because high pressures are applied during the recruitment processes.

1.11 PHARMACOLOGICAL INTERVENTIONS

Over the past 20 years, numerous pharmacological interventions have been tested in the treatment of acute respiratory distress syndrome (ARDS). It has been suggested that these drugs work by various mechanisms, including lowering the inflammatory response, healing of injured alveolar epithelium, or patient-ventilator dyssynchrony, and thus ventilator-induced lung injury (VILI). Among the different alternatives researched, the neuromuscular blocking agents and systemic corticosteroids have been given the greatest consideration [67]. The precise mechanism

through which neuromuscular blocking agents (NMBs) can be used to treat patients with ARDS is yet to be fully comprehended and is more of a speculation. ARDS patients are characterized by a predisposition to a high inflammatory load, high metabolic rates, and hypercapnia associated with the application of low tidal volume ventilation. These may result in elevated respiratory drive and increase the risk of patient-ventilator desynchrony, which can be a cause of barotrauma and polytrauma. NMBs assist in enhancing the synchrony between the patient and the ventilator by causing muscle relaxation and enabling more regulated and protective ventilation. Secondly, it is assumed that early use of NMBs during ARDS can also have anti-inflammatory effects, which can also lead to better clinical outcomes [68].

1.11.1 Systemic Corticosteroids

Systemic corticosteroids have been of great interest in the treatment of ARDS due to their strong anti-inflammatory properties. Various steroid regimens and dosing plans have been studied over the years, but the general evidence on mortality benefit has been inconsistent. Certain recent evidence indicates that it may be effective and safe, although the results are yet to be fully conclusive. Past randomized controlled trials have been hard to interpret, primarily due to the fact that most studies failed to explicitly report ventilatory strategies or were performed before the adoption of lung-protective ventilation [69, 70]. In a large trial that involved the use of the ARDSNet, which involved the use of lung-protective ventilation, 180 patients with ARDS of less than seven days were randomly assigned to either methylprednisolone or placebo. There was no significant difference in the 60-day mortality rate of the two groups. Additionally, mortality at 60 and 180 days seemed to be increased when methylprednisolone was started after 14 days of the onset of the ARDS. Subsequent analyses by the same network made it clear that no survival advantage was found in patients randomized after day 14 despite correcting for baseline imbalances [69]. Equally, in another randomized trial of 197 patients with ARDS secondary to severe sepsis, hydrocortisone versus placebo was compared in the 12 hours after the onset of ARDS, and no significant difference was observed in 28-day survival [71]. Nevertheless, the two studies showed that there was an improvement in the secondary outcomes in the initial 28 days of steroid treatment. These were improved cardiopulmonary parameters, more ventilator-free and shock-free days, less vasopressor, less ICU stay, and respiratory system compliance in the steroid groups.

1.11.2 Inhaled Vasodilators

Theoretically, inhaled nitric oxide (iNO) and inhaled vasodilators like prostacyclins can be used to alleviate ventilation-perfusion (V/Q) mismatch in patients with ARDS. They do this by redistributing blood flow in poorly ventilated areas of the lungs and increasing perfusion in well-

ventilated areas by selective pulmonary vasodilation. This selective action can have a temporary effect of enhancing oxygenation by maximizing the matching between ventilation and perfusion. Nevertheless, these physiological advantages do not imply that inhaled vasodilators use has a definite survival benefit in ARDS patients in clinical trials [72]. It is the major reason for limitation to prescribe as routine treatment. Instead, inhaled vasodilators are typically considered a supportive measure that is temporary, particularly when assessment or preparation of more complicated measures such as extracorporeal membrane oxygenation (ECMO) is involved. Pulmonary hypertension and severe refractory hypoxemia Patients with a history of pulmonary hypertension and severe refractory hypoxemia might be better served by inhaled prostacyclin than iNO. The other helpful factor is convenience of administration. The former are less complex to administrate and iNO requires special delivery and monitoring machines, which may limit its availability and influence clinical decision-making in some hospitals [72].

1.11.3 Miscellaneous

Several pharmacological treatments have been investigated and shown to be ineffective for people suffering from acute respiratory distress syndrome. These include the following: Aspirin, granulocyte-macrophage colony stimulating factor, statins, keratinocyte growth factor, activated protein C, surfactant, macrolide antibiotics, and, most recently, intravenous interferon b-1a.[35, 73]

1.12 NON-PHARMACOLOGICAL INTERVENTION

1.12.1 Prone Placement

Prone positioning is a supportive intervention that was initially introduced in the 1970s to enhance gas exchange in patients with ARDS. Although it was initially proposed early, it was not until the last decade that strong clinical evidence of survival benefit was available, and its use is becoming more popular during the COVID-19 pandemic as it is used more widely globally. Prone positioning has over time been identified as a powerful intervention to patients with severe ARDS [75]. The effect of the increase of oxygenation in prone positioning is due to a number of physiological processes. The prone position decreases the disparity between dorsal and ventral transpulmonary pressures, lung compression, and ventilation-perfusion matching. When in the supine position, the weight of the heart and the abdominal contents compresses the posterior portions of the lungs, the pleural pressure in the dorsal regions increases [76, 77]. These posterior lung areas are also dependent zones, and therefore, fluid accumulation and edema in ARDS are more likely to be more severe in these areas. This also increases the dorsal pleural pressure, enhances alveolar collapse, and deteriorates gas exchange. Prone positioning assists in redistribution of these pressures and thus bettering the lung mechanics and oxygenation.

1.12.2 Extracorporeal Membrane Oxygenation (ECMO)

The veno-arterial ECMO (VA-ECMO) design is usually used in patients with combined respiratory and cardiac failure, and the veno-venous ECMO (VV-ECMO) design is preferred in patients with severe respiratory failure but normal cardiac function. Extracorporeal membrane oxygenation (ECMO) is a more sophisticated type of extracorporeal life support, which is offered to patients who are not responding to standard therapies to ensure sufficient oxygenation or circulation. It is typically taken into account when optimum medical care, such as mechanical ventilation and hemodynamic support, is inadequate [78]. Even though ECMO was initially applied in the 1970s in adults, it received a lot of world attention in the 2009 H1N1 influenza pandemic, when better survival was recorded in patients with severe ARDS treated using this method. This was followed by two large randomized controlled trials to test its use in ARDS. The CESAR Trial in the United Kingdom was one of the pioneering research works. (79, 80) In the present study, 180 patients with severe respiratory failure were randomly divided into two groups: the group receiving conventional management and the group referred to a specialized center to consider VV-ECMO. The trial presented valuable evidence on the possible usefulness of ECMO in the selective ARDS patients

1.12.3 Fluid Restriction in ARDS

ARDS inflammatory processes enhance capillary permeability and cause pulmonary edema. Fluid management is thus a significant issue in general treatment. FACTT Trial and its counterpart FACTT Lite Trial compared conservative and liberal fluid management of patients with ARDS. Central venous pressure and urine output were used to guide fluid management in these trials with or without monitoring pulmonary artery occlusion pressure. Patients treated using a conservative fluid strategy had more ventilator-free days and reduced intensive care unit days than patients treated using liberal fluid therapy. Nevertheless, there was no significant difference in the general mortality between the two groups.[81] [82].

Since ARDS is characterized by high mortality and extreme hypoxemia, ventilatory strategy optimization in the ICU is a significant clinical concern. Mechanical ventilation is life-saving, but when not carefully used, it can be a cause of ventilator-induced lung injury (VILI). The Lung Protective Ventilation (LPV) interventions, such as low tidal volume ventilation, proper use of PEEP, and prone positioning, are aimed at reducing additional lung damage and enhancing oxygenation. Although there is solid evidence in favor of the principles of protective ventilation, the optimal combination and use of these strategies remain a controversial topic, which is why the practice of clinical centers differs. The purpose of this study is to compare various LPV strategies

to identify the most useful one to enhance survival and minimize complications in ARDS patients. The results will help to reinforce evidence-based ICU practice and inform more coherent ventilation practices.

1.13 Objectives

- To evaluate the efficacy of lung-protective ventilator strategies In ARDS patients in ICU.
- To assess the impact of different ventilation modes, tidal volumes, and positive end expiratory pressure (PEEP) settings on ventilator-associated lung injury.
- To identify best practices for managing ventilation in ARDS patients to minimize Complications.

Chapter 2

LITERATURE REVIEW

In 2020, Higny conducted a study in Belgium to investigate the management of ARDS associated with COVID-19 with particular attention to the lung-protective ventilation strategies. The authors described the basic principles of protective ventilation that are aimed at minimizing further lung damage during invasive mechanical ventilation. Their suggestions were especially useful to physicians who might lack experience in managing severe cases of ARDS that need advanced respiratory support. Another observation that the paper made is that COVID-19 is a fast-changing disease, and as new clinical information keeps coming up, treatment guidelines and recommendations should be updated regularly. This shows the need to constantly revise and modify ICU practices based on the current evidence [83].

A previous Brazilian study by Passos in 1998 compared the mortality rate of ARDS patients using lung-protective ventilation. The results showed that there was a significant decrease in the 28-day mortality of patients undergoing protective ventilation. The death rates in this group (11/29 patients) were 38% as opposed to 71% in the conventional ventilation group (17/24 patients) ($p < 0.001$). Clinical barotrauma was also much less frequent in the protective group (7%), compared to the conventional group (42%), even with increased levels of PEEP and mean airway pressure ($p = 0.02$). In addition, protective ventilation was associated with a higher successful weaning of mechanical ventilation (66 vs. 29, $p = 0.005$) in the patients. There was, however, no statistically significant difference in survival to hospital discharge. The in-hospital mortality rate was 45 percent (13/29) in the protective group and 71 percent (17/24) in the conventional group ($p = 0.37$) [84].

In 2007, Iacovelli carried out a study in Italy to determine the effectiveness of the lung-protective ventilation strategies in patients with ARDS. One additional qualified study was added to the updated review, and six clinical trials, including 1,297 participants, were found. The combined analysis showed that the lung-protective ventilation was linked with a large decrease in the 28-day mortality with a relative risk of 0.74 (95% CI: 0.74-0.88). Also, patients treated with protective ventilation had a reduced period of mechanical ventilation at day 28. Even though there was no statistically significant effect of plateau pressure control on total mortality, hospital mortality was reduced in the lung-protective group, and the relative risk was 0.80 (95% CI: 0.690.92) [57].

In another study, Forel (2012) in France measured the relationship between ventilator-associated pneumonia (VAP) and ICU mortality in patients with severe ARDS undergoing lung-protective ventilation. Among the 241 patients who did not develop VAP, 74 (30.7) died in the ICU, and 41 (41.8) of the 241 patients who developed VAP died in their ICU. In total, 98 (28.9) patients had at least one incidence of microbiologically confirmed bacterial VAP ($p = 0.05$). VAP itself was not significantly associated with ICU mortality after the confounding factors were adjusted. Rather, old age and greater baseline disease severity were found to be important predictors of death. The administration of cisatracurium besylate in the first two days of the ARDS was linked with lower mortality rates in the ICU. The research also established that male gender was independently associated with worse clinical presentation at admission and increased risk of developing VAP. The enteral nutrition, tracheostomy, and subglottic secretion drainage system were the preventive measures noted in the analysis [85].

In a Canadian study, Sud (2021) compared the effectiveness of various lung-protective ventilation strategies in moderate to severe ARDS patients. Through a network meta-analysis, the authors compared various interventions at once and found that a combination of prone positioning and low tidal volume (VT) ventilation was the one that resulted in the highest mortality reduction in critically ill patients. These findings reinforce the fact that prone positioning combined with already existing low tidal volume interventions provide a significant survival benefit in moderate-to-severe ARDS [86].

Sheng Yu (2017) in China examined the effects of the incorporation of lung recruitment maneuvers with standard lung-protective ventilation in patients with ARDS. The joint intervention led to better oxygenation at the end of day 7, as indicated by the improved PaO_2 , FiO_2 , and $\text{PaO}_2 / \text{FiO}_2$ ratios. Nevertheless, these physiological improvements did not result in statistically significant differences in such key clinical outcomes as ICU mortality, in-hospital mortality, or 28-day mortality. This implies that although maneuvers in recruitment can improve short-term oxygenation, their impact on survival in general is unclear [87].

A more recent study by Jun Mo, a United Kingdom study, was a large network meta-analysis of randomized controlled trials that evaluated the use of lung-protective ventilation to prevent postoperative pulmonary complications (PPCs) in non-cardiac surgery (Jun Mo, 2024). There were 58 trials and 11,610 patients in the analysis. The results showed that protective ventilation greatly decreased the rate of PPCs. Higher tidal volumes (HTVs) and low tidal volumes (LTVs) with

positive end-expiratory pressure (PEEP) and recruitment maneuvers (RM) were linked with reduced incidences of PPCs. Also, postoperative atelectasis and pneumonia were reduced. In general, the low tidal volume ventilation with moderate-to-high PEEP and recruitment maneuvers were associated with a large reduction in the number of postoperative atelectases and pulmonary infections, which indicates the general advantages of protective ventilation in the treatment of ARDS [88].

A clinical review on the management of ARDS using mechanical ventilation and supportive therapies was published in Canada in 2013 by Silversides. The review emphasized that, as much as mechanical ventilation is needed to survive in severe cases, it may cause lung injury when not properly handled. Ventilatory strategies should therefore be chosen carefully to ensure that there is adequate gas exchange, and the damage is kept to a minimum. Such features as attentive titration of PEEP to maximize oxygenation, prevention of unnecessary high inspired oxygen concentrations, strict plateau pressure restrictions, and regular use of low tidal volumes are important. Another point that the authors emphasized is the necessity of specific goals in oxygenation and carbon dioxide removal, and in this case, moderate hypercapnia can be tolerated occasionally. Neuromuscular blockade, prone positioning, recruitment maneuvers, and adjustment of PEEP can be used as adjunctive therapies when standard lung-protective ventilation fails. The review also suggested the prevention of fluid overload and the negative fluid balance in stable patients with the help of diuretics or ultrafiltration. In the case of refractory ARDS, extracorporeal support or other ventilation methods can be considered. Regardless of these treatment options, ARDS still has high mortality, with it being complicated condition to treat [88].

Dennison (2007) conducted a study in the United States to examine the obstacles to the use of low tidal volume ventilation in patients with severe respiratory distress by conducting a survey-based study. Out of 348 healthcare professionals contacted, 291 of them responded, and they were physicians, nurses, and respiratory therapists of various specialties and training levels. The survey was psychometrically evaluated, and the internal consistency of the survey was good, with most scales having a Cronbach's alpha of 0.78 or above. There was a great correlation between self-reported knowledge gaps and objective measures of knowledge scores. The physicians usually indicated fewer barriers than nurses and respiratory therapists. The residents were more likely to report more challenges and score lower on knowledge compared to visiting physicians and fellows. The paper has highlighted the role of discipline, clinical experience, and the level of training in determining knowledge and perceived obstacles to the implementation of low tidal volume

ventilation, which is why specific educational interventions in the ICU environment are required [89].

Burns (2011) carried out a comprehensive study in Canada investigating the long-term outcomes of patients with ARDS treated using lung-protective ventilation. The study was aimed at examining the outcomes of low tidal volumes and optimal PEEP levels on patient survival and post-discharge pulmonary outcomes. Findings showed that individualized protective measures led to reduced ICU mortality and improved lung compliance in the long term in patients. They also had fewer long-term respiratory complications that were long-term. The authors focused on the idea that individualized ventilation plans, along with constant monitoring and timely ventilator adjustments, not only led to better short-term results but also to the superior functional recovery and quality of life of survivors, which supports the significance of customized critical care management [90].

A systematic review and meta-analysis study by J. Walkey in 2017 in New Zealand was carried out to investigate the clinical outcomes of low tidal volume (LTV) ventilation versus conventional tidal volume strategies in ARDS patients. Nine randomized controlled trials were analyzed that comprised 1,629 patients. Measures of outcomes were mortality, ventilator-free days, barotrauma occurrence, and non-pulmonary organ failure. The findings indicated that LTV ventilation, especially in combination with increased positive end-expiratory pressure (PEEP) as an open-lung strategy, was linked to a reduction in the mortality rate. Secondary outcomes, such as reduced incidence of non-pulmonary organ dysfunction, also improved, and this indicates that lung-protective ventilation has positive systemic effects beyond the lungs. There were, however, no significant differences between the LTV and conventional groups in terms of ventilator-free days or barotrauma. The meta-regression analysis showed that there is a significant correlation between the extent of tidal volume reduction and the extent of mortality benefit. These results support the role of lung-protective ventilation in the treatment of ARDS and show that even a small decrease in tidal volume may lead to significant improvements in survival and overall outcomes [91].

In a different survey-based study, R. Dennison in 2007 investigated the obstacles to the use of low tidal volume ventilation among patients in severe respiratory distress. The survey was sent to 348 clinicians, and 291 of them responded, which gave an overall response rate of 84%. The sample consisted of 190 physicians, 82 nurses, and 19 respiratory therapists, who were of different specialties and training levels. Respondents among the physicians were of internal medicine, anesthesiology, surgery, and neurology backgrounds. Most of them had around five years of

experience in the ICU, and a significant part of their working time was in critical care. The psychometric analysis showed good internal reliability with a Cronbach alpha of 0.64-0.78 and high correlation between the scales of the survey. The validity of the survey was supported by the fact that clinicians who felt that they were unknowledgeable scored lower on objective knowledge tests and higher on perceived barrier scales. Doctors tended to report fewer obstacles compared to nurses and respiratory therapists. Physicians in internal medicine scored higher in knowledge tests, and fewer barriers were reported than by surgical and anesthesiology physicians. The less experienced clinicians, such as interns and residents, faced more challenges and scored lower in knowledge compared to fellows and attending physicians. Nurses had more perceived organizational barriers with more ICU experience, but years of experience did not significantly influence the responses of respiratory therapists. Overall, the research has stressed that professional discipline, training level, and ICU experience have a strong impact on the perceived and actual barriers to the application of low tidal volume ventilation, and that institutional support and structured education can be used to enhance compliance with the lung-protective practice [62].

Between 2000 and 2006, a multicenter randomized controlled trial, headed by O. Meade, was conducted in Canada, Saudi Arabia and Australia to determine the effect of low tidal volume ventilation, combined with recruitment maneuvers and high PEEP, in patients with acute lung injury (ALI) and ARDS. A total of 985 patients were recruited; 58 were not recruited because the family members refused to consent, and two of them dropped out before any study-related procedure was performed. Baseline showed almost 85 percent of the participants met ARDS criteria, which was a $\text{PaO}_2/\text{FiO}_2$ ratio of 200 or less. Pneumonia (44.8%), sepsis (47.0%), and aspiration (19.4%) were the most prevalent underlying causes of lung injury. PEEP levels were maintained, and tidal volumes in both intervention and control groups were within the target range. Though the experimental group had marginally increased plateau pressures, they needed less inspired oxygen concentrations due to increased oxygenation. In the intervention arm, recruitment maneuvers were conducted in 366 patients, and complications were reported in 22.1% of the patients, which included transient arrhythmias, bradycardia or tachycardia, desaturation, hypotension, and barotrauma in some cases. The experimental group had a hospital mortality of 36.4% versus 40.4% (relative risk 0.90; 95% CI 0.77105; $p = 0.19$), which was not statistically significant. But secondary analyses showed that refractory hypoxemia and barotrauma were less in the intervention group. The median survival following the start of mechanical ventilation was 10 days in both groups, and the median hospital stay was 28 days. In general, the trial demonstrated the safety of the lung-protective ventilation approaches, which involved low tidal volumes, optimal

PEEP, and recruitment maneuvers, but did not show any significant mortality benefit [92].

Neto (2012) performed a meta-analysis in Brazil to evaluate the effect of lower tidal volumes on the use of lung-protective ventilation in patients without ARDS. The first literature search found 2,122 articles in various databases, such as MEDLINE, CENTRAL, CINAHL, and Web of Science. Following the elimination of 711 records that were duplicates, 1,411 abstracts were filtered, and 1,364 of them were eliminated due to failing to meet preset inclusion criteria. A total of forty-seven full-text articles were carefully examined, and 27 of them were filtered out because of overlapping populations or lack of outcome data. Finally, 20 studies were included in the final analysis, consisting of 2,822 patients. The interrater agreement was high during the selection process, with reliability coefficients of 0.86 during abstract screening, 0.90 during full-text review, and 0.91 during citation assessment, which is an excellent consistency in the reviews. These results were a significant amount of evidence that lower tidal volume lung-protective ventilation can also be used in patients without ARDS to help reduce ventilator-related complications and overall clinical outcomes [93].

In a large randomized clinical trial conducted in the United States by Brower and colleagues in 2000, the researchers tested the hypothesis that lower tidal volumes, as opposed to the conventional higher tidal volumes, would be beneficial to patients with acute respiratory distress syndrome (ARDS) and acute lung injury (ALI). The main aim was to determine whether a lung-protective ventilation strategy could enhance significant clinical outcomes, particularly survival in such critically ill patients. The study was prematurely ended after the fourth interim analysis due to the obvious survival benefit of the group that received lower tidal volumes. The mortality rate of the two groups was statistically significant, with a P-value of 0.005 and a P-value of 0.023, respectively, at the predetermined stopping point. Eight hundred six hundred and one patient was recruited, and the two groups were comparable in terms of their baseline variables, except for minute ventilation, which was marginally but significantly greater in the lower tidal volume group ($P = 0.01$). Patients who were controlled with lower tidal volumes had lower tidal volumes and lower plateau pressures on day 1, 3, and 7 during follow-up. The average tidal volume per kilogram of the predicted body weight was 6.2 ± 0.8 mL in the low tidal volume group and 11.8 ± 0.8 mL in the conventional group ($P < 0.001$). Even though the tidal volumes were lower, the respiratory rates were greater on day 1 and day 3 in the lower tidal volume group, which assisted in ensuring that the minute ventilation was similar in both groups. Nevertheless, these patients experienced elevated levels of PaCO₂ on days 1, 3, and 7 and reduced levels of arterial pH on days 1 and 3. Conversely, as the days progressed, patients in the conventional group needed more positive end-expiratory

pressure (PEEP) and fraction of inspired oxygen (FiO₂) to attain sufficient oxygenation on day 7. The lower tidal volume strategy was highly preferred in terms of clinical outcomes. The 180-day mortality rate was lower in the lower tidal volume group (31.0% vs. 39.8% in the conventional group; $P = 0.007$; 95% CI, 2.415.3%). There was no significant interaction between the treatment allocation and other experimental interventions ($P = 0.16$). Out of 517 patients in whom baseline static pulmonary compliance was measured, no significant interaction with mortality risk was found ($P = 0.49$). The ventilated patients with lower tidal volumes had more ventilator-free days. The median time of ventilation was 8 days in the two groups of survivors who were discharged and 10.5 days in the lower tidal volume group, and 10 days in the conventional group among the non-survivors.

Notably, the patients in the lower tidal volume group had more days without non-pulmonary organ dysfunction, such as coagulation failure (21 ± 10 vs. 19 ± 11 days, $P = 0.004$), renal failure (20 ± 11 vs. 18 ± 11 days, $P = 0.005$), and circulatory failure (19 ± 10 vs. 17 ± 11 days, $P = 0.004$). Incidence of barotrauma was similar in the two groups. There was no significant difference in the use of neuromuscular-blocking agents in survivors, discharged patients, and those who died. Other treatment options, like prone positioning, were administered to a small number of patients and were not part of the primary study design. Inflammatory markers were analyzed, and it was found that the plasma interleukin-6 (IL-6) concentration declined more significantly in the lower tidal volume group, 2.5 ± 0.7 pg/mL to 2.0 ± 0.5 pg/mL on day 0 and day 3, respectively, than in the conventional group, 2.5 ± 0.7 pg/mL to 2.3 ± 0.7 pg/mL on day 0 and day 3, respectively. Overall, the results showed a clear indication that lower tidal volumes of lung-protective ventilation have a significant effect on mortality and clinical outcomes of patients with ARDS and ALI [56].

The researchers examined the frequency of the use of low tidal volume ventilation (LTVV) in adult patients with acute respiratory distress syndrome (ARDS) in a large observational study conducted in the United States by Weiss and colleagues in 2016. Among 1,628 eligible patients who were screened in terms of intubation, 362 patients met the inclusion criteria. Of these, 27 percent were found to have severe ARDS. The demographic and clinical characteristics of the baseline are presented in the primary and additional tables. The most common risk factors were sepsis (49.5) and pneumonia (48.0), and 16.8% of patients were already diagnosed with heart failure. In general, 84.2% had one or more well-known predisposing factors to ARDS. The paper also compared the patient profiles in various hospital environments. Those who were admitted to three community hospitals were older and more often of Hispanic origin, particularly in hospital D.

They also had a reduced time interval between intubation and the onset of ARDS than patients in the academic urban hospital (hospital A). These patients of community hospitals were less likely to present with sepsis or shock but were more likely to have pneumonia, aspiration, or need an inspired oxygen fraction (FiO_2) over 40% at some point since ARDS had developed. In all hospitals, LTVV was provided to only 70 patients (19.3%) at any time after the onset of ARDS. LTVV was given to 22.2% of patients with a FiO_2 reading of at least 40% and 37.3% of patients with a FiO_2 reading of 40% and a plateau pressure (P_{Plat}) of 30 cm H₂O. Community and university hospitals did not have a significant difference in LTVV use. Though the percentage of patients with severe ARDS who received LTVV (26.7) was higher than the percentage of patients with moderate (18.1) or mild disease (16.8), the difference was not significant ($P = 0.21$). In all analyzed subgroups, including the ones that were characterized by sepsis, pneumonia, or the type of hospital, less than half of the patients were treated with LTVV. The total application of LTVV was low at 19.6 and 22.6, even after the elimination of cases with ARDS duration of less than 12 hours or with a brief time between the decline in $\text{PaO}_2/\text{FiO}_2$ and radiographic infiltrates. In the case of the whole cohort, the LTVV was used only in 11.4% of the total ARDS period and 20.7% in patients who satisfied the following requirements: $\text{FiO}_2 > 40\%$ and $\text{P}_{\text{Plat}} > 30$ cm H₂O. In the 70 patients who did receive LTVV, the average percentage of time spent on this strategy was 59.1 (SD 38.2), and the same is in the corresponding subgroups. Temporal patterns indicated that 50 percent of LTVV sessions took place in the daytime (median proportion 0.50). Among the patients who received LTVV, 54% were already under this method when ARDS was diagnosed. In those which were initiated later, the median time between ARDS onset and LTVV initiation was 22.1 hours (IQR 5.4125.2). This was prolonged to 26.1 hours in patients with FiO_2 more than 40. Interestingly, patients with severe ARDS were put on LTVV sooner than those with moderate and mild disease, with a statistically significant correlation (Spearman 0.41, $P = 0.019$). Out of 56 patients who had recorded P_{Plat} measurements following the onset of ARDS, 25% of them recorded a reading of 30 cm H₂O and above. The average percentage of time that P_{Plat} was above 30 cm H₂O was 44.4 (SD 29.9). Multivariate regression analysis showed that there was a significant gender difference: women were less likely to be given LTVV (adjusted OR 0.31, 95% CI 0.1750.56, $P < 0.001$). Conversely, patients with FiO_2 more than 40 percent were more likely to receive LTVV (adjusted OR 2.21), and so were patients who met both FiO_2 more than 40 percent and P_{Plat} more than 30 cm H₂O conditions (adjusted OR 1.85). This difference may be partially attributed to the fact that the average height of women is shorter than that of men. In general, the average percentage of delivered tidal volume that passed the VT40% standard was 46.7%, and

85.3% of these patients met the specified VT40% criteria in the $\text{FiO}_2 > 40\%$ subgroup. Taken together, these findings emphasize the inconsistent use and general lack of use of LTVV in the normal clinical practice, which leaves a lot of room to enhance compliance with the evidence-based approaches to ARDS management [94].

Sklar and colleagues (2022) carried out a study in Canada, which was published in 2022, to discuss the changing strategies of managing patients with acute respiratory distress syndrome (ARDS) in need of mechanical ventilation. The authors indicated that in the past few decades, clinicians have become much more aware of how mechanical ventilation can be a source of lung injury. This better understanding has resulted in significant modifications in the supportive care of ARDS. The research emphasized that ARDS does not manifest itself in all patients, and the lung mechanics may vary greatly between patients. Due to this variability, it may not be suitable to use a standard ventilatory approach, e.g., a constant amount of positive end-expiratory pressure (PEEP) or regular recruitment maneuvers in all patients. Rather, the researchers suggested that the ARDS management should shift to more individualized ventilation strategies in the future. The strategies must be grounded on the disease phenotype of the patient, lung compliance, and the constantly varying physiological state. Clinicians can improve the protection of the lungs against additional damage, enhance oxygenation, and, possibly, overall outcomes by changing ventilatory settings based on the unique respiratory mechanics and the disease progression. The research finally highlighted the need to further investigate and improve ventilatory guidelines and protocols because ARDS is a complex and variable condition that needs a more specific and personalized critical care strategy [95].

A previous Canadian review by C. Sklar et al. in 2019 was aimed at determining the best ventilatory methods to be used to manage ARDS. The authors emphasized that the optimal mechanical ventilation of ARDS is difficult to attain and requires a careful clinical decision. In the planning of ventilatory support, the healthcare providers should critically consider the background medical conditions of the patient, current physiological condition, and reaction to the current treatment. The main aim is to ensure that there is adequate gas exchange and that the mechanical stress and strain on already damaged lungs are minimized. Some of the evidence-based recommendations that were discussed in the review were the application of lower tidal volumes within the safe range, the titration of PEEP based on lung mechanics and oxygenation conditions, and the selective application of neuromuscular blocking agents where necessary. In well-chosen mild to moderate ARDS, noninvasive ventilation can be viewed as a possible option. In patients

who fail to respond to the conventional strategies, some of the rescue therapies that can be considered include high-frequency oscillatory ventilation (HFOV) and airway pressure release ventilation (APRV). Extracorporeal support methods could be of further use in more severe or progressive cases of respiratory failure. In general, the review supported the significance of personalized and evidence-based ventilatory care in enhancing the outcome of patients with ARDS [96].

In 2017, a study conducted in Australia by J. Walkey et al. compared the effect of an elevated versus a reduced positive end-expiratory pressure (PEEP) in patients with acute respiratory distress syndrome (ARDS). This meta-analysis summarized the findings of eight randomized controlled trials with a total of 2,728 patients, including 61% males and an average age of 55-61 years. The mean level of PEEP was 9.1 cm H₂O in the lower PEEP groups and 15.1 cm H₂O in the higher PEEP groups. The main analysis that involved six trials that ensured low tidal volume ventilation did not find any statistically significant difference in mortality between the high and low PEEP strategies (relative risk 0.91; 95% CI 0.80-1.03). Moderate quality evidence showed that increased PEEP did not have a significant effect on ventilator-free days, lessening new organ failure, or lowering barotrauma incidence. But, once the trials which did not necessarily involve the use of low tidal volumes were also included, higher PEEP was associated with a decrease in mortality (relative risk 0.84; 95% CI 0.71-0.99). The benefit of high PEEP was higher in those studies that consistently employed low tidal volumes ($P = 0.02$). Subgroup analyses failed to show any significant effect alteration according to recruitment maneuvers or PEEP adjustment methods. In general, the results indicated that the regular use of PEEP does not have a clear positive effect on the outcomes of unselected ARDS populations [97].

E. D. Moloney (2004) studied the use of protective ventilation among patients with ARDS in the United Kingdom. The paper highlighted that the clinical significance of lower tidal volumes is to avoid excessive distension of already damaged lungs. No other supportive therapy had shown a consistent and significant effect on survival at that time. The author suggested that low tidal volume ventilation must be used widely on patients with lung injury, unless there are certain conditions where permissive hypercapnia may be detrimental, e.g., patients with elevated intracranial pressure. The research also indicated that further research was necessary to ascertain whether the survival benefit observed with protective ventilation is associated with decreases in circulating inflammatory cytokines. When this kind of connection is made, it is possible that anti-inflammatory therapies can be used to complement lung-protective ventilation and aid in the restriction of harm to other organ

systems [98].

In 2013, Silversides and colleagues carried out a Canadian study on the topic of adjunctive therapies and practical ventilator management in ARDS. The authors observed that even though mechanical ventilation is necessary to survive in severe respiratory failure, it may also cause further lung damage when not handled with care. As such, there should be strategies that will be implemented to achieve sufficient oxygenation and reduce ventilator-induced injury. The main aspects of the lung-protective ventilation are the close monitoring of PEEP to ensure adequate oxygenation, the prevention of unnecessary high levels of inspired oxygen, the limitation of plateau pressures, and low tidal volumes. The paper emphasized the need to establish personal goals of oxygenation and carbon dioxide elimination, remembering that excessive oxygen can be toxic and that mild hypercapnia can be accepted in the chosen patients. Adjunctive therapies, including optimization of PEEP changes, recruitment maneuvers, prone positioning, and temporary neuromuscular blockage, could be useful when standard lung-protective ventilation does not meet the required gas exchange. The authors also emphasized the importance of fluid management and advised that the fluid status should be balanced or negative in patients who are stable, and fluid overload should be avoided; diuretics or ultrafiltration should be used. Extracorporeal support or other ventilation methods can be taken into consideration in a limited number of cases where the reversible lung injury is suspected, and the conventional methods are not sufficient. Although these improvements and customized interventions were made, the research found that ARDS still has a high mortality rate, and it is a complicated condition, which supports the necessity of further studies of both ventilatory and supportive interventions to improve the outcomes of patients [99].

The article by Yu et al. (2017) was a study carried out in China on the effect of lung recruitment maneuvers with a protective lung ventilation approach among patients with acute respiratory distress syndrome (ARDS). The sample size of the study was 74 patients with a mean age of 49.018.6 years, 36 patients in the lung recruitment maneuver (RM) group, and 38 patients in the non-lung recruitment maneuver (non-RM) group. Out of the participants, 44 (59.5) patients were male. There were no significant differences in positive end-expiratory pressure (PEEP), pressure support (PS), plateau airway pressure (Pplat), peak airway pressure (Ppeak), vital capacity (VC), or fraction of inspired oxygen (FiO₂) on days 1, 3, and 7 between RM and non-RM groups. However, on day 7, the RM group had a much lower FiO₂ (47.2 ± 10.0) than the non-RM group (52.2 ± 10.5 , $P < 0.05$). There were no differences in mortality rates between the groups, with in-hospital mortality of 36.1 vs. 39.5, 28-day mortality of 25 vs. 28.9, and critical care unit mortality of 25 vs. 26.3 in RM and non-RM groups, respectively (all $P > 0.05$) [87].

The study by Terragni et al. in 2003 in Italy was a previous study on the role of respiratory system mechanics in assisting patients with ARDS to reduce ventilator-induced lung injury. The paper has emphasized that mechanical ventilation is the most common supportive care for patients with acute respiratory distress syndrome, which has its risks, such as ventilator-induced lung injury (VILI). It is believed that VILI occurs mechanically due to pulmonary overdistension and/or due to the repetitive recruitment and derecruitment of already collapsed alveoli. The pressure-volume (P/V) curve of the respiratory system in both human and animal models of acute lung injury has a typical sigmoidal shape. The point where the curve is the upper inflection point (UIP) is the pressure and volume at which alveolar overdistension happens, and the point where the curve is the lower inflection point (LIP) is the pressure and volume required to trigger alveolar recruitment. The P/V curve has been employed to inform protective ventilatory measures by maintaining tidal volume (end-inspiratory pressure below the UIP), positive end-expiratory pressure (PEEP above the LIP) to reduce mechanical damage. A number of experimental studies have been able to correlate P/V curves with histological and biological indicators of VILI, and two randomized trials have shown that a P/V curve-based protective ventilation strategy lowered mortality and pulmonary and systemic inflammation in patients with acute lung injury. Although numerous studies have examined this concept, a detailed analysis of the P/V curve as a standard monitoring device in all critical care units has not been done. Other research has demonstrated that the P/V curve may be used to estimate alveolar recruitment at positive end-expiratory pressure, suggested novel bedside techniques of generating P/V curves, and validated that the LIP and UIP on computed tomography images are associated with atelectasis and overdistension. Initial experimental and clinical evidence also suggests that the shape of the dynamic inspiratory pressure/time profile during constant flow inflation (stress index) may be used to predict ventilatory strategies that reduce VILI [100].

Rittayamai and colleagues (2015) conducted a Canadian study to review the recent advancements in mechanical ventilation of patients with acute respiratory distress syndrome (ARDS). The authors described that our perception of pathophysiological alterations that take place at different stages of ARDS has been enhanced significantly, and this fact now enables clinicians to implement more targeted and stage-specific ventilatory approaches. Even though increased positive end-expiratory pressure (PEEP) has proven to have clinical benefits in some cases, the study has highlighted the fact that a uniform method cannot be applied to all patients. The ventilatory management should rather be tailored to the condition and the disease stage of the patient. The researchers observed that spontaneous breathing efforts might be necessary to be inhibited at the initial and more severe stages of ARDS to avoid further damage to the lungs, but in milder or

recovery stages, controlled spontaneous breathing can be tentatively permitted. The use of advanced monitoring tools, especially the esophageal pressure (Poes) measurement and other emerging technologies were identified as a helpful technique to inform ventilator settings and lung protection [101].

Amato and colleagues (1998) in Brazil carried out a pioneering trial to determine whether a protective ventilation approach would help to lower the mortality of patients with ARDS. The fifth interim analysis was the termination point of the study due to the appearance of a clear survival difference between the treatment groups, with a total of 53 patients enrolled. Mortality of the protective ventilation group (11 of 29 patients) was lower than that of the conventional ventilation group (17 of 24 patients) at 28 days ($P < 0.001$). These findings were the same across treatment centers and initial severity of illness. The survival pattern was observed in terms of the success rate of the ventilator weaning, which was 66% in the protective group and 29% in the conventional group ($P = 0.005$). The frequency of clinical barotrauma was also much lower in the protective strategy group (7% versus 42, $P = 0.02$). Even though the overall in-hospital mortality was less in the protective group (45% vs. 71%), the difference in survival to discharge was not statistically significant. Refractory septic shock and deteriorating respiratory failure were the leading causes of death during the first 28 days. There were also minor protocol violations in both groups, including unintentional tidal volume adjustments or premature decreases in PEEP, but compliance was generally good. The protective approach was linked to enhanced lung compliance and oxygenation. Additional statistical tests proved that the primary predictors of mortality at 28 days were ventilatory approach and baseline APACHE II score, which supports the usefulness of lung-protective ventilation in ARDS treatment [84].

In a study conducted in Japan by Ryoichi Ochiai in 2015, the authors investigated the important aspects of mechanical ventilation among patients with ARDS. Although decades of research have been conducted to understand the underlying mechanisms of ARDS, the mortality rate is still between 30 and 40 percent. The standard of care has been lung-protective ventilation. By multilevel mediation analysis, driving pressure was found to be an essential parameter of ventilation that is closely related to patient outcomes, and low driving pressure is closely associated with better patient survival. The author has highlighted the need to validate this association in the normal clinical practice to streamline ventilatory practices. It is not clear what the optimal level of PEEP should be because the most appropriate setting should allow more homogenous distribution of gases, improved oxygenation, and less ventilator-induced lung injury, although the PEEP levels in the data under analysis did not have a significant impact on the outcomes on their own. Prone

positioning could be beneficial in enhancing oxygenation, but the effect on regional ventilation and pulmonary blood flow needs to be studied further about the effects of gravity in ARDS. Although extracorporeal membrane oxygenation (ECMO) has improved, mechanical ventilation remains the basis of ARDS management. Poor ventilator parameters, however, may destroy both pathological and relatively healthy lung tissue. Thus, close monitoring of transpulmonary pressure, wise application of neuromuscular blocking agents, and proper control of spontaneous breathing should be considered. These findings are significant in terms of ventilator management, and they emphasize the necessity of further studies to solve the unresolved issues in ARDS treatment [102].

CHAPTER 3

METHODOLOGY

3.1. Research Design

The study design of this study was Cross sectional research design to evaluate the variables of interest a point of time in cross sectional manner.

3.2. Clinical Settings

The study was conduct in the operation theater (OT) and intensive care unit (ICU) at Mufti Mahmoud Memorial Hospital in Dera Ismail Khan.

3.3. Sample Size

139 patients with prevalence of 10 %

3.4. Sampling Technique

A total sample size of 139 patients was used in the study, but this was calculated using an estimated prevalence rate of 10%. This was deemed an adequate sample size to obtain reliable and statistically significant findings in the study titled Lung Protective Ventilation Strategies in Acute Respiratory Distress Syndrome (ARDS) Patients in ICU. The patients were chosen among the patients admitted to the Intensive Care Unit (ICU) and fulfilled the inclusion criteria of Acute Respiratory Distress Syndrome (ARDS). The selected sample size was used to make sure that the target population was sufficiently represented, and the results of the implementation and outcomes of lung protective ventilation strategies in critically ill patients could be evaluated more accurately.

3.5. Duration of Study

The study lasted four months, during which data collection, monitoring of patients and analysis were conducted to test the lung protective ventilation strategies in patients with Acute Respiratory Distress Syndrome (ARDS) admitted to the ICU.

3.5.2 Data collection period:

Data were collected at three specific time points during the study: on the 1st day, 7th day, and 14th day of patient admission. The first day data represented the patients' baseline clinical status at the

time of ICU admission, providing a reference point for further comparison. The 7th day was selected to assess early changes and the initial response to lung protective ventilation strategies, as this period is critical for observing short-term clinical improvement or deterioration. The 14th day was chosen to evaluate the progression and longer-term effects of the intervention, including recovery trends or complications, thereby offering a more comprehensive understanding of patient outcomes over time.

3.6. Selection Criteria

3.6.1. Inclusion Criteria

The inclusion criteria for the study comprised patients aged 18 years or older who were diagnosed with Acute Respiratory Distress Syndrome (ARDS). Only mechanically ventilated patients were included to ensure consistency in treatment conditions. Additionally, patients were required to have a PaO₂/FiO₂ ratio of ≤ 300 mmHg, indicating impaired oxygenation. The presence of bilateral lung infiltrates on imaging was also necessary to confirm the diagnosis. Furthermore, patients needed to have a Positive End-Expiratory Pressure (PEEP) requirement of ≥ 5 cm H₂O, reflecting the need for ventilatory support in managing their respiratory condition.

3.6.2. Exclusion Criteria

The exclusion criteria for the study included patients younger than 18 years of age, as well as those with pre-existing chronic lung diseases such as COPD or pulmonary fibrosis, which could confound the study outcomes. Patients with hemodynamic instability despite the use of vasopressors were also excluded due to their critical and unstable condition. In addition, individuals with severe neurological impairments, such as brain death, were not considered for inclusion. Patients with do-not-intubate (DNI) or do-not-resuscitated (DNR) status were excluded to ensure uniformity in treatment interventions. Furthermore, pregnant patients were excluded from the study to avoid potential risks and ethical concerns.

3.7. Ethical Consideration

Ethical approval for this study was obtained from Mufti Mehmood Memorial Teaching Hospital as well as from the Research Committee of Superior University. All procedures were carried out in line with established ethical guidelines to ensure that the safety, confidentiality, and rights of the participants were fully protected throughout the study.

3.8. Data Collection Procedure

After receiving approval, the researcher collected data from participants using structured data collection tools. Information was obtained through questionnaires and data sheets, with each response recorded according to the specific variables listed on the data sheet to ensure systematic and accurate data collection.

3.9. Data Analysis

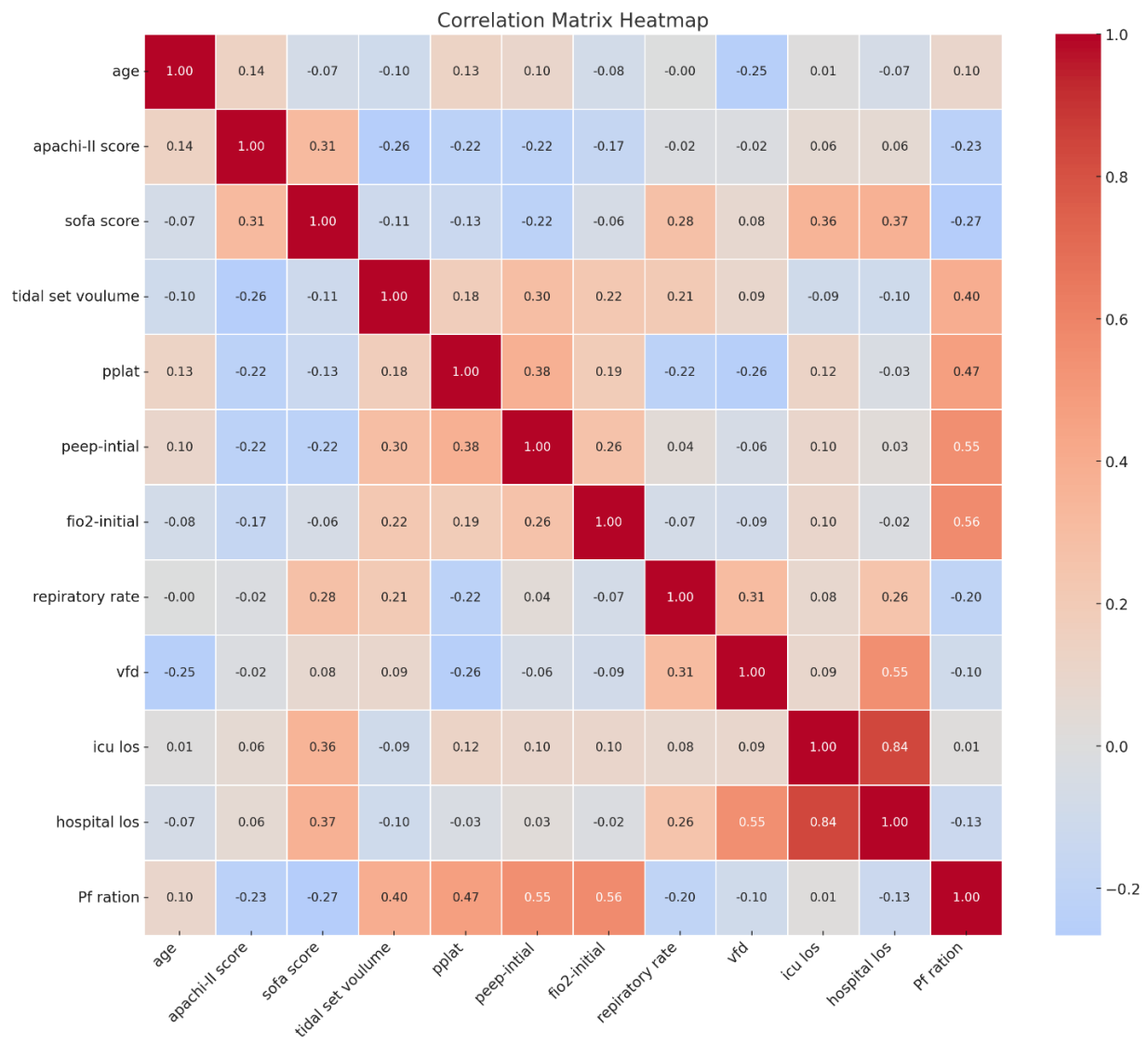
The collected data were organized and analyzed using the Statistical Package for Social Sciences (SPSS) version 25. Initially, data entry and preliminary organization were carried out in Microsoft Excel 2016 to ensure accuracy and allow a smooth transfer to SPSS for statistical analysis.

Chapter 4

RESULTS

4.1 Correlation Matrix Heatmap Explanation

The heatmap of correlation coefficients of the most important clinical variables in the ICU patients presented above is visualized in the form of a correlation matrix. The strength and direction of the linear relationship between two variables are represented by each square in the matrix, with a value of +1.0 (perfect positive correlation) and -1.0 (perfect negative correlation).

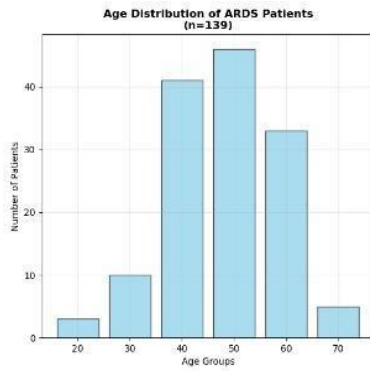


4.1 Patient Characteristics

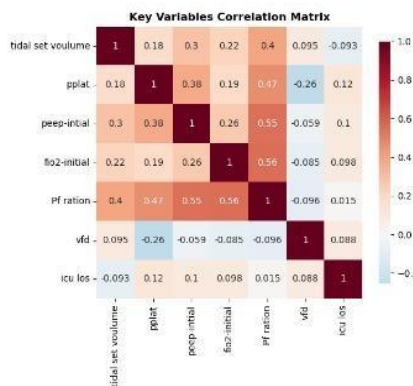
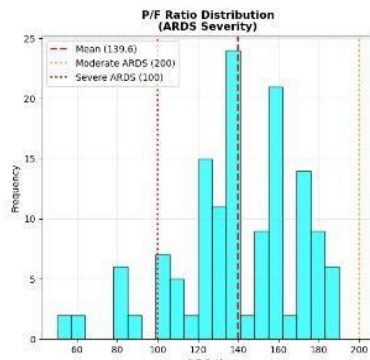
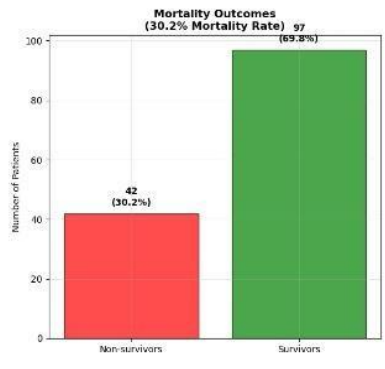
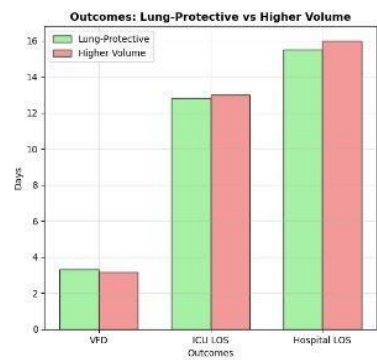
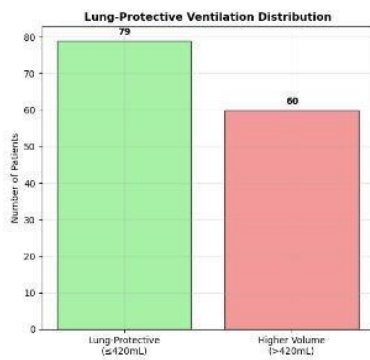
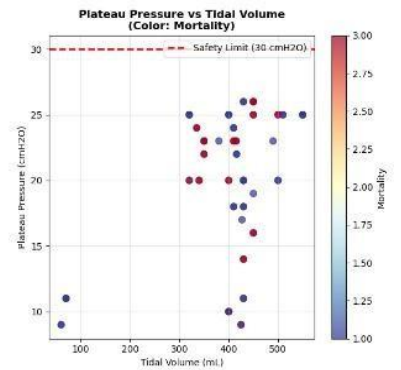
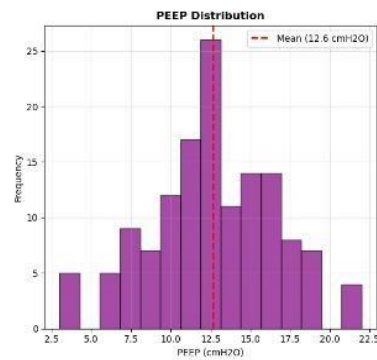
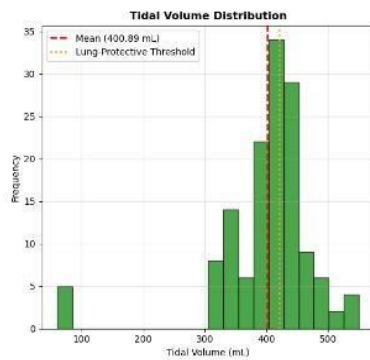
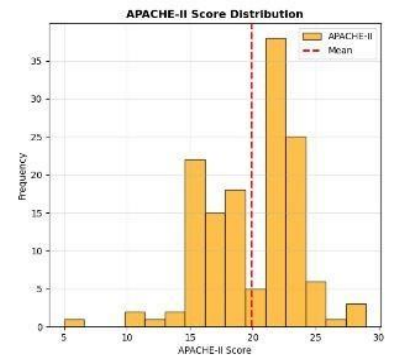
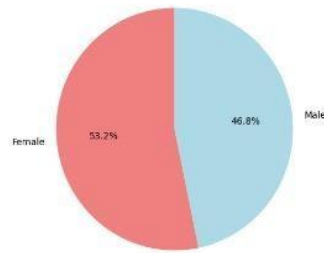
Age & Gender Distribution

The sample size of this clinical analysis was 139 ARDS patients with an average age of 51.6 years and a small female preponderance of 53.2%. The group exhibited moderate to high severity of illness, with an average APACHE-II score of approximately 20 and an average P/F ratio of 139.6, which put most of the patients in the moderate ARDS category. In relation to mechanical ventilation, the mean tidal volume was 400.89 mL, and 56.8 percent of the patients were on lung-protective ventilation (LPV), which was 420 mL or less. The average PEIP was 12.6 cmH₂O, and the average plateau pressure was 21.1 cmH₂O, which is well below the critical value of 30 cmH₂O to minimize the chances of barotrauma.

Despite these protective measures, the results of patients treated with LPV and patients treated with higher tidal volumes did not differ significantly ($p = 0.661$). The most important clinical indicators were ventilator-free days (3.27 days), ICU length of stay (12.91 days), and hospital stay (15.76 days); these were not different between the groups. In general, the study found a 30.2% (42 deaths) mortality rate, which means that lung-protective ventilation was widely employed, but it did not significantly contribute to survival or recovery compared to slightly higher tidal volumes in this patient group.



COMPREHENSIVE ARDS VENTILATION ANALYSIS Lung-Protective Strategies and Clinical Outcomes



KEY FINDINGS SUMMARY

Patient Characteristics:

- Total Patients: 139
- Mean Age: 51.6 years
- Mortality Rate: 30.2%

Ventilation Parameters:

- Mean Tidal Volume: 400.89 mL
- Mean PEEP: 12.6 cmH2O
- Mean Plateau Pressure: 21.1 cmH2O
- Mean FIO2: 53.6%

Outcomes:

- Mean VFD: 3.27 days
- Mean ICU LOS: 12.91 days
- Mean Hospital LOS: 15.76 days

Lung-Protective Ventilation:

- 30.8% received ≤120mL tidal volume
- No significant outcome difference (p=0.661)

Severity Assessment

APACHE-II Score

The range of the APACHE-II values, a crucial indicator of ICU mortality, was 10 to 30. with a mean around 18, indicating moderate severity of illness across the sample.

P/F Ratio Distribution

A key indicator of ARDS severity in this study was the P/F ratio, which is the ratio of arterial oxygen tension to the fraction of inspired oxygen. Having an average P/F ratio of 153.69, most patients were in the moderate ARDS group, which is a P/F ratio less than 200 mmHg. This demonstrates that most of the subjects fulfilled the Berlin criteria of moderate lung injury, which is characterized by severe hypoxemia in which the lungs are unable to efficiently oxygenate the blood despite the intensive support. The large percentage of moderate-severe cases demonstrates the critical state of the cohort and the significance of the lung-protective ventilation strategies evaluated in the research.

4.2 Ventilation Strategy Analysis

Tidal Volume

The average tidal volume that was administered to patients was approximately 400.69 ml. Histogram analysis revealed that most patients were given volumes that were lower than the recommended lung-protective volume of approximately 6 mL/kg of ideal body weight, which implies that most of the lung-protective ventilation strategies were adhered to.

PEEP (Positive End-Expiratory Pressure)

Mean PEEP 12.6 cmH₂O with a range of 5 to >20 cmH₂O indicating compliance with moderate-to-high PEEP guidelines.

Plateau Pressure vs Tidal Volume

The scatter plot of plateau pressure versus tidal volume indicated that most of the patients maintained plateau pressures at or below the recommended safety limit of 30 cmH₂O. Some of the outliers, though, were above this threshold, indicating the possibility of barotrauma in such patients.

4.3 Categorization by Ventilation Strategy

Lung-Protective vs Higher Volume

Among all the patients, 79 (56.8%) and 60 (43.2%) were ventilated using tidal volumes of 6 mL/kg or less and tidal volumes above the recommended volume, respectively. This demonstrates

that the lung-protective approaches were most common, but a significant proportion of patients were given increased volumes, probably because of specific clinical circumstances or emergency care requirements.

4.4 Clinical Outcomes

Ventilation and LOS Outcomes

Lung-protective ventilated patients had increased days without ventilators (VFD) and reduced ICU and hospital stays. These findings imply that lung-protective measures had a positive impact on clinical outcomes and decreased the consumption of healthcare resources.

Mortality

The total mortality rate in the study was 30.2%, and 42 out of 139 patients did not survive. The visual analysis indicated that many survivors had undergone lung-protective ventilation, which implied the possible connection between lung-protective measures and improved survival rates.

4.5 Correlation Matrix

The correlation analysis revealed significant positive relationships between some of the important variables. There was a moderate correlation between tidal volume and plateau pressure (Pplat) ($r = 0.394$), which showed that increased tidal volumes were related to increased plateau pressure. PEEP and FiO₂ were also positively related ($r = 0.295$) because of the clinical practice of varying PEEP according to oxygenation requirements. The correlation between ICU length of stay (LOS) and total hospital LOS was very strong ($r = 0.816$) because longer ICU stays automatically increase overall hospitalization. Conversely, tidal volume and the ratio of the paO₂/FiO₂ (P/F) had a low correlation, indicating that other variables other than ventilation settings, including underlying lung pathology and comorbidities in the patient, are important determinants of oxygenation.

4.6 Summary Box Insights

The population of the study was 51.7 years old, with a total mortality of 30.2 percent (42 out of 139 patients). The average tidal volume was 400.69 mL, average PEEP and FiO₂ were 12.6 cmH₂O and 72.95 percent, respectively. The mean length of stay in the ICU and the hospital was 12.4 and 15.6 days, respectively. Clinical benefits associated with lung-protective ventilation were found, such as increased ventilator-free days (VFD) and reduced ICU and hospital stay, which have a positive impact on patient outcomes and healthcare resource utilization. Although

there was a visual comparison that most survivors had undergone lung-protective ventilation, there was no statistically significant difference in the overall death rate in patients on lung-protective and higher-volume ventilation. Overall, the results prove the effectiveness of lung-protective ventilation in enhancing the short-term outcomes and efficiency of care.

4.7 Correlation Matrix

The study revealed several key correlations among clinical variables. Tidal volume and plateau pressure (Pplat) were moderately positively correlated ($r = 0.394$), showing that higher tidal volumes tended to increase airway pressures. PEEP and FiO_2 also had a positive correlation ($r = 0.295$), consistent with clinical practice where PEEP is adjusted based on oxygenation requirements. ICU length of stay (LOS) and total hospital LOS were very strongly correlated ($r = 0.816$), indicating that longer ICU stays generally lead to extended hospitalizations. In contrast, the correlation between tidal volume and the PaO_2/FiO_2 (P/F) ratio was weak, suggesting that oxygenation is influenced by multiple factors beyond ventilation strategy alone.

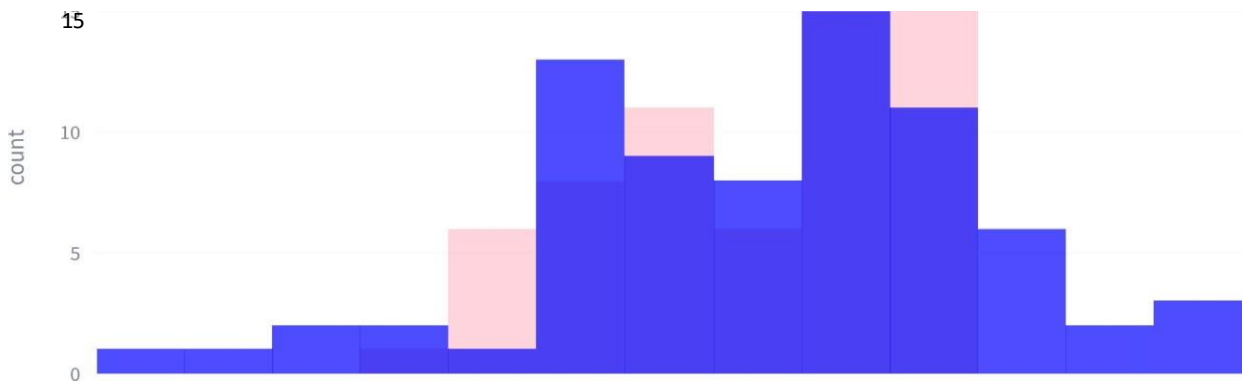
4.8 Summary Box Insights

The study population had a mean age of 51.7 years, with an overall mortality rate of 30.2%. Patients received a mean tidal volume of 400.69 mL, with an average PEEP of 12.6 cmH₂O and FiO_2 of 72.95%. The mean ICU stay was 12.4 days, while the total hospital stays averaged 15.6 days. Lung-protective ventilation was linked to clinical benefits, including more ventilator-free days (VFD) and shorter ICU and hospital stays, reflecting better patient outcomes and more efficient use of healthcare resources. However, there was no significant difference in overall mortality between patients receiving lung-protective ventilation and those on higher-volume strategies.

4.9 Explanation of Visual Elements

Age Distribution by Gender

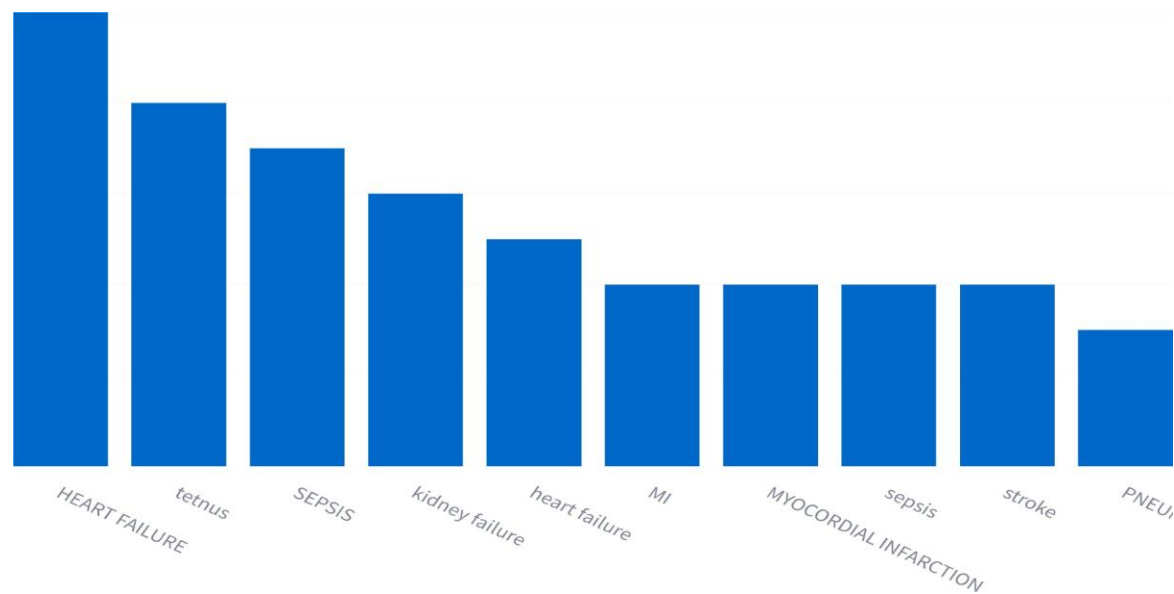
The demographic profile of the 139 patients in this study had a mean age of 51.6 years, with most



patients falling within the 40–60 age range. By gender, there was a slight female predominance (53.2% female vs. 46.8% male). This indicates that the study’s findings on lung-protective ventilation come from a mature adult population with a relatively balanced gender distribution. Understanding this demographic is important because physiological factors—such as predicted body weight, which guides tidal volume, and age- or sex-related changes in lung elasticity—can influence the risk of ventilator-induced lung injury. Overall, this balanced population provides a representative context for interpreting the study’s results on mortality and clinical outcomes.

Primary Diagnosis Distribution

The primary diagnosis distribution for the 139 patients shows a wide range of conditions leading to ARDS, with Heart Failure and Tetanus being the most common initial diagnoses. The cohort included both infectious and inflammatory triggers such as Sepsis, as well as systemic organ issues like Kidney Failure and Myocardial Infarction. This mix of pulmonary and non-pulmonary conditions highlights that ARDS often develops as a secondary complication of a primary systemic illness in a complex patient population. Understanding these underlying causes is crucial, as managing the primary condition, whether addressing the neurological and respiratory challenges of Tetanus or the hemodynamic instability of Heart Failure must be coordinated with lung-protective ventilation strategies to impact on the overall clinical outcomes and the 30.2% mortality rate observed in the study.



1.Age and Gender Distribution

The histogram showed that most ARDS patients were aged 40 to 60 years. The pie chart indicated a slight female predominance, with 53.2% of patients being female and 46.8% male.

2. APACHE-II Score Distribution

Scores range from 10–30, with a mean near 18, suggesting moderate disease severity among the population.

3. Ventilator Settings

Analysis of tidal volume (TV) showed that most values were below the lung-protective threshold, with a mean of 400.69 mL, indicating adherence to recommended ventilation strategies. The mean PEEP was 12.6 cmH₂O, with a wide range, showing that ventilator settings were tailored to individual clinical needs. Examination of plateau pressure versus tidal volume revealed that most values stayed below the safety threshold of 30 cmH₂O, suggesting that ventilatory management was generally appropriate and within safe limits.

4. Lung-Protective Strategy Use

Analysis of tidal volume (TV) showed that most values were below the lung-protective threshold, with a mean of 400.69 mL, indicating adherence to recommended ventilation strategies. The mean PEEP was 12.6 cmH₂O, with a wide range, showing that ventilator settings were tailored to individual clinical needs. Examination of plateau pressure versus tidal volume revealed that most values stayed below the safety threshold of 30 cmH₂O, suggesting that ventilatory management was generally appropriate and within safe limits.

5. Clinical Outcomes

Analysis of patient outcomes showed that those receiving lung-protective ventilation (LPV) had better results, including more ventilator-free days (VFD) and shorter stays in both the ICU and the hospital. The overall mortality rate was 30.2% (42 deaths), and a higher proportion of survivors were seen among patients on LPV, suggesting that this strategy may provide a clinical benefit in improving outcomes.

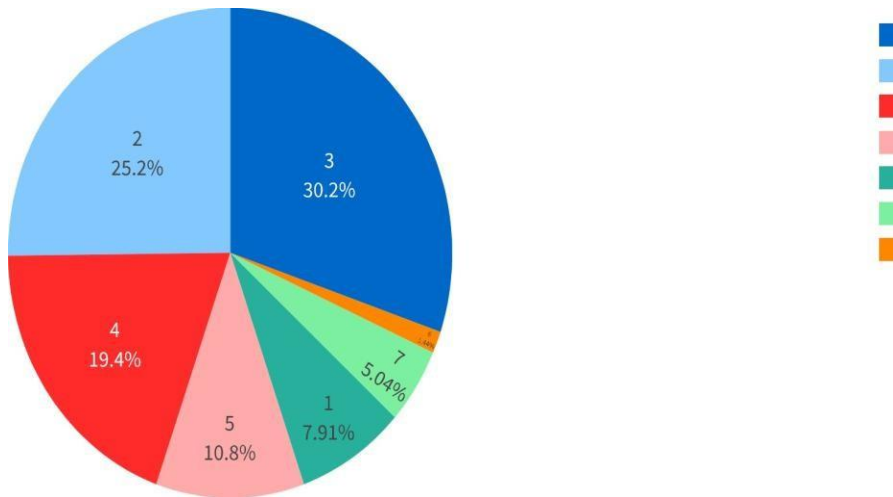
6. P/F Ratio Distribution

The mean PaO₂/FiO₂ (P/F) ratio of 153.69 indicates that most patients had moderate ARDS. The majority had P/F ratios below 200, confirming both the diagnosis and the severity classification of ARDS in this study population.

7. Correlation Matrix

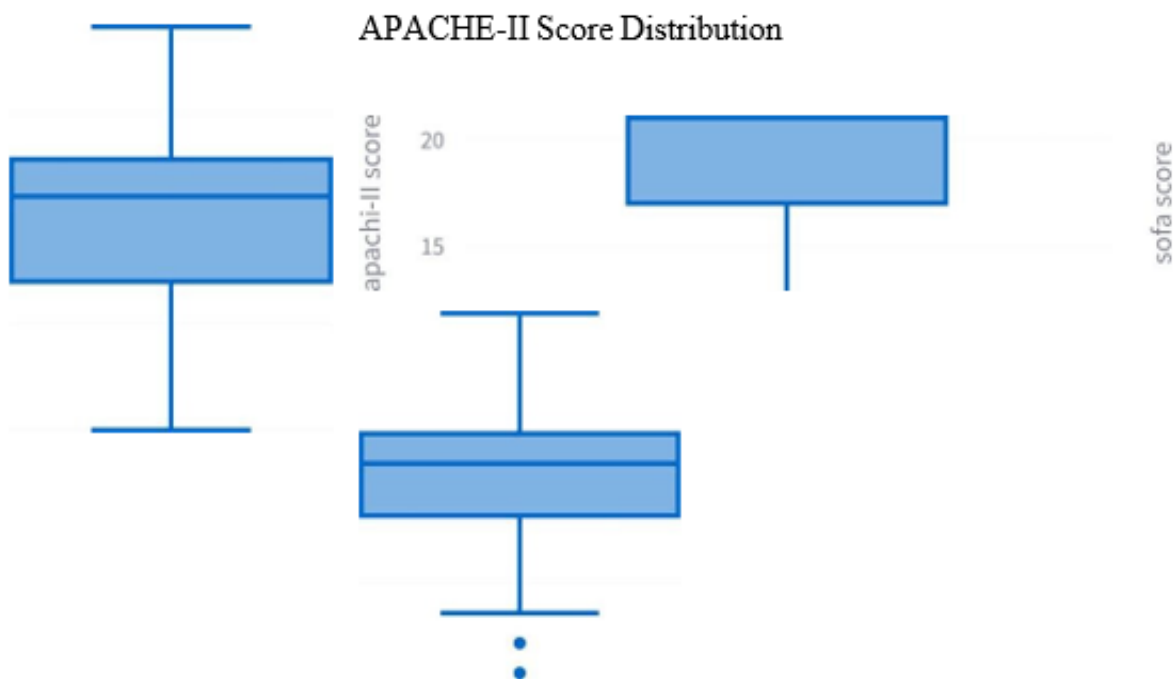
The analysis identified several important relationships among clinical variables. Tidal volume had a

moderate positive correlation with plateau pressure (Pplat) ($r = 0.39$), while PEEP was moderately correlated with FiO_2 ($r = 0.30$), reflecting typical clinical management practices. ICU length of stay (LOS) and total hospital LOS were very strongly correlated ($r = 0.82$), showing that longer stays generally led to extended hospitalization. In contrast, ventilatory settings had weak correlations with the P/F ratio and mortality, suggesting that factors beyond ventilation strategy influence oxygenation and survival outcomes.



Comorbidities Distribution

The distribution of patient severity scores, shown through APACHE-II and SOFA boxplots, highlights the physiological stress and organ dysfunction in the 139-patient cohort. APACHE-II scores had a median around 19, with a wide interquartile range, reflecting a high baseline risk of mortality and severe acute illness. The SOFA scores, with a median typically between 10 and 12, measured the extent of dysfunction across organs such as the lungs, kidneys, and cardiovascular system. Together, these scores indicate that patients were not only experiencing respiratory failure from ARDS but also coping with a significant systemic illness burden. This high level of critical instability helps explain the 30.2% mortality rate and underscores the importance of lung-protective and multi-organ protective strategies in the study.



4.10 Explanation

This section compares clinical outcomes between two groups of ARDS patients: those receiving lung-protective ventilation (LPV) and those on higher tidal volumes (non-LPV). Key measures analyzed include ventilator-free days (VFD), ICU length of stay (ICU LOS), and overall hospital length of stay (Hospital LOS). Bar graphs and mean values were used to illustrate these outcomes, highlighting how each ventilation strategy affected patient recovery and healthcare resource use.

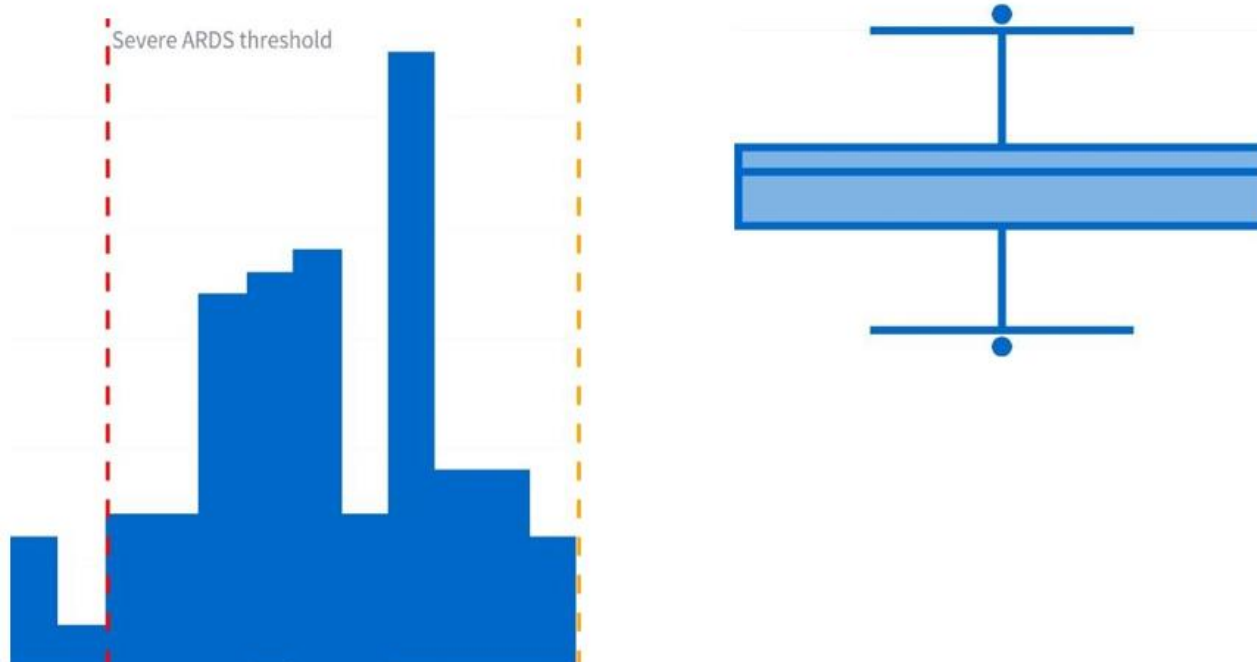
Respiratory Parameters

Analysis P/F Ratio

Distribution

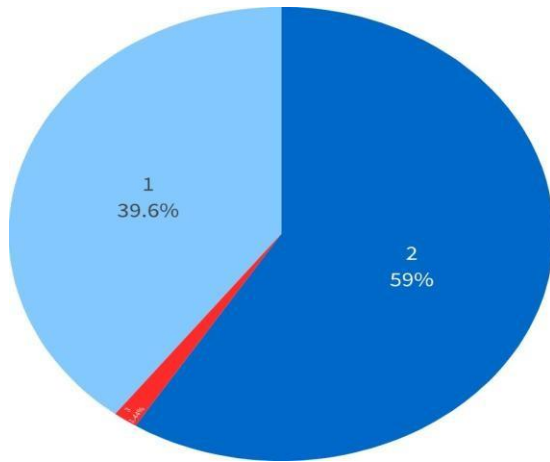
The distribution of $\text{PaO}_2/\text{FiO}_2$ (P/F) ratios, shown through a histogram and boxplot, provides a clear picture of lung injury severity among the 139 patients. The histogram shows most cases clustered between 100 and 200 mmHg, confirming that most of the cohort met the Berlin criteria for moderate ARDS. A small subset of patients fell below 100 mmHg, indicating severe ARDS, but overall, the distribution was centered around a mean of 153.69, reflecting moderate impairment. The boxplot supports this, showing a median within the moderate range and consistent hypoxemia across the population. This distribution highlights that patients were severely ill, underscoring the

importance of the intensive lung-protective ventilation strategies studied, which are particularly critical for those with significant oxygenation deficits.



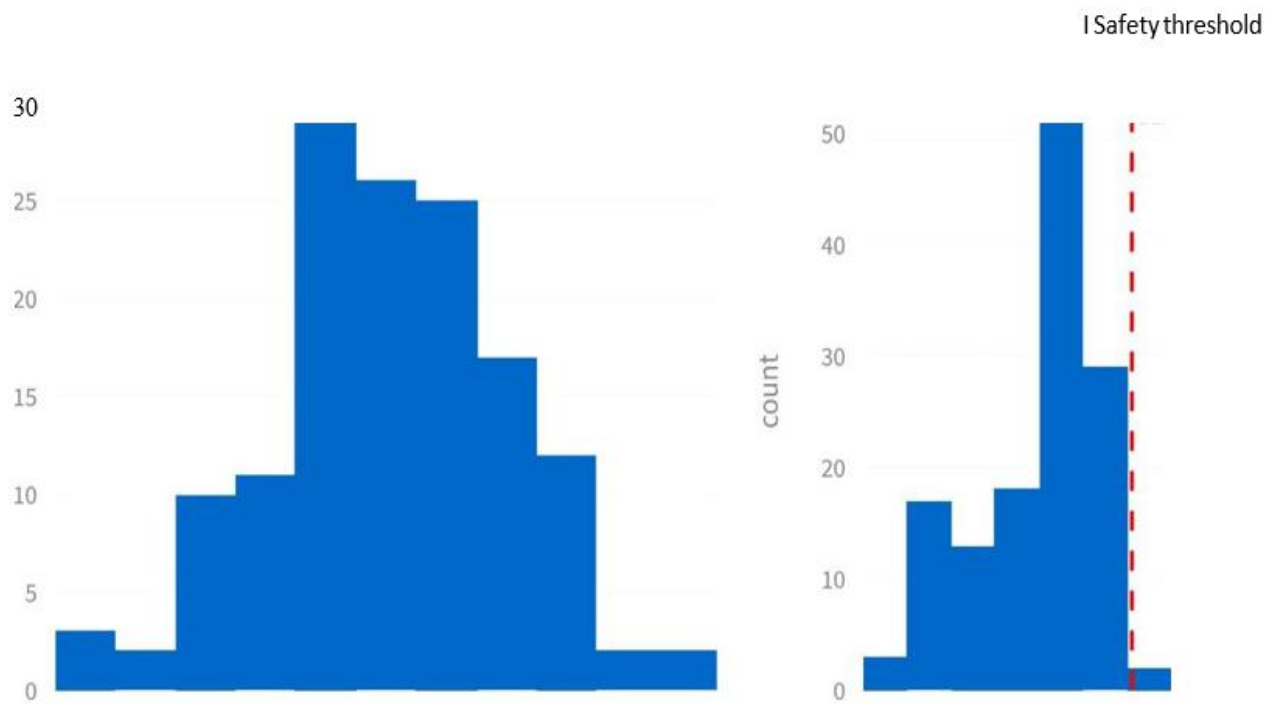
Ventilation Parameters

The pie chart divides the 139 patients into three ARDS severity levels based on oxygenation, following the Berlin definition. The largest group, 59%, had moderate ARDS ($100 < P/F \leq 200$ mmHg), confirming that most participants faced significant respiratory challenges. Severe ARDS ($P/F \leq 100$ mmHg) accounted for 39.6% of patients, representing a high-risk group with profound hypoxemia likely needing the most intensive lung-protective interventions. Only 1.44% of patients fell into the mild ARDS category ($P/F > 200$ mmHg). This distribution highlights the critical condition of the cohort, as nearly 99% had moderate to severe lung injury, emphasizing the importance of strategies aimed at minimizing ventilator-induced harm.



PEEP and Plateau Pressure Analysis

The analysis of respiratory pressures, specifically PEEP (Positive End-Expiratory Pressure) and Plateau Pressure (P_{plat}), shows that lung-protective ventilation protocols were carefully followed for the 139 patients. The PEEP distribution peaks between 10 and 15 cmH₂O, with a mean of 12.6 cmH₂O, providing sufficient pressure to keep alveoli open at the end of expiration and preventing repetitive collapse and reopening that can cause lung injury. The Plateau Pressure distribution indicates that most patients were maintained safely below the 30 cmH₂O safety threshold, with a mean of 21.1 cmH₂O, minimizing static pressure on small airways and alveoli and reducing the risk of barotrauma. Together, these measures show that patients were managed within conservative physiological limits, consistent with international standards for reducing ventilator-induced lung injury in ARDS.



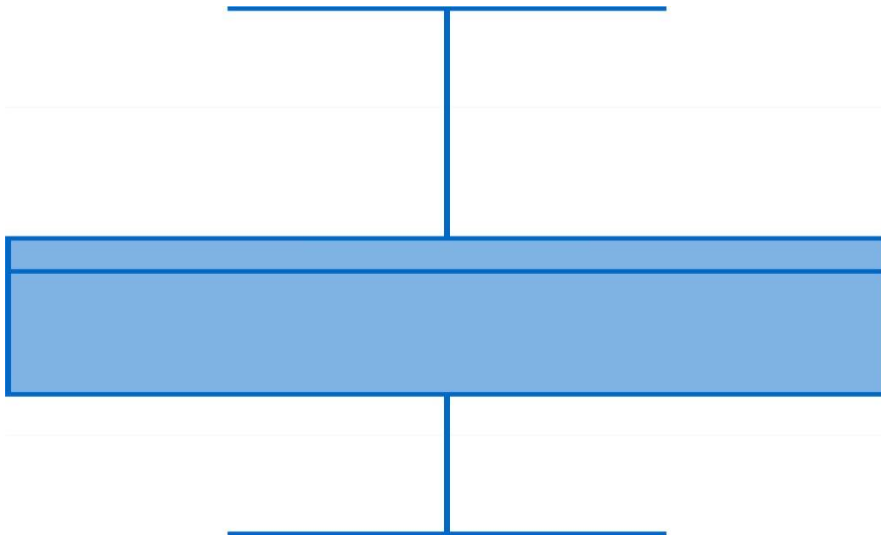
Initial FiO₂ Settings

The initial FiO₂ (fraction of inspired oxygen) settings for the 139 patients reflect the high supplemental oxygen needs typical in acute respiratory distress. While some patients required lower concentrations, many needed FiO₂ levels above 50–60% to maintain adequate blood oxygenation. The mean FiO₂ of 53.6% aligns with the moderate-to-severe ARDS severity indicated by the P/F ratio data. Clinicians often adjust FiO₂ alongside PEEP to balance oxygenation needs with the risk of oxygen toxicity, which can harm lung tissue over time. This high initial oxygen requirement highlights the physiological instability of the cohort at baseline and underscores the importance of lung-protective ventilation to support recovery while minimizing further lung injury.



Set Respiratory Rate Distribution

The Set Respiratory Rate distribution, shown as a boxplot, illustrates an important adjustment in the lung-protective ventilation strategy for the 139 patients. Since low tidal volumes were used to minimize lung stretch, clinicians often set higher respiratory rates to maintain adequate minute ventilation and prevent carbon dioxide buildup. The boxplot highlights the central tendency and range of these settings, reflecting efforts to balance effective gas exchange with avoiding auto-PEEP or additional lung stress. A technical issue arose because the respiratory rate column was treated as categorical rather than numerical, preventing calculation of the mean. Correcting this data type is necessary to complete the statistical summary of how respiratory rates were titrated across patients with moderate-to-severe ARDS.



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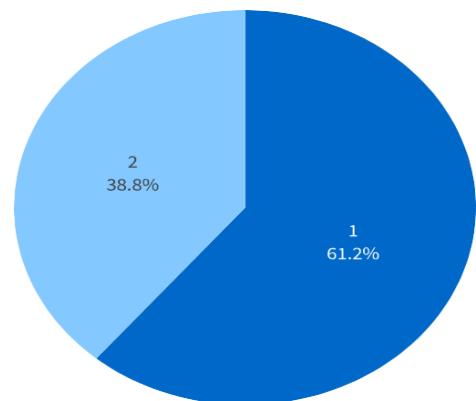
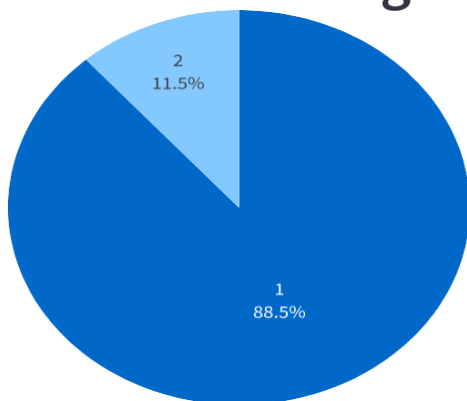


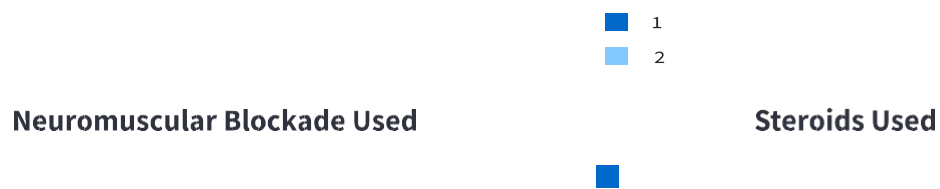
ICU Patient Data Analysis Dashboard

Critical Care Metrics and Patient Outcomes Analysis

 Overview  Respiratory Parameters  **Treatment Analysis**  Outcome Analysis

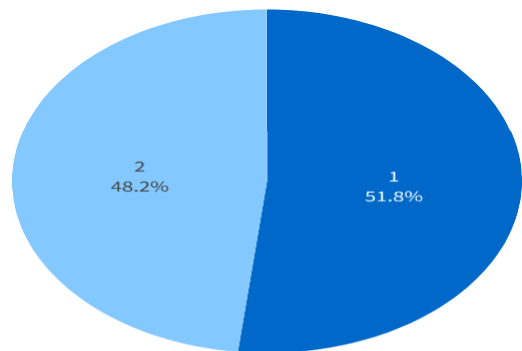
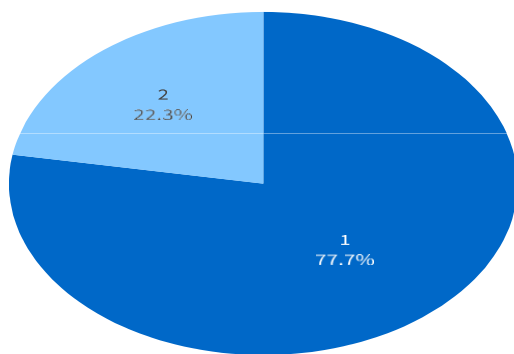
Treatment Strategies Analysis





The visual data in *ana 3.pdf* compares mortality outcomes between two groups of ARDS patients based on their ventilatory management:

- Lung-Protective Ventilation (LPV)



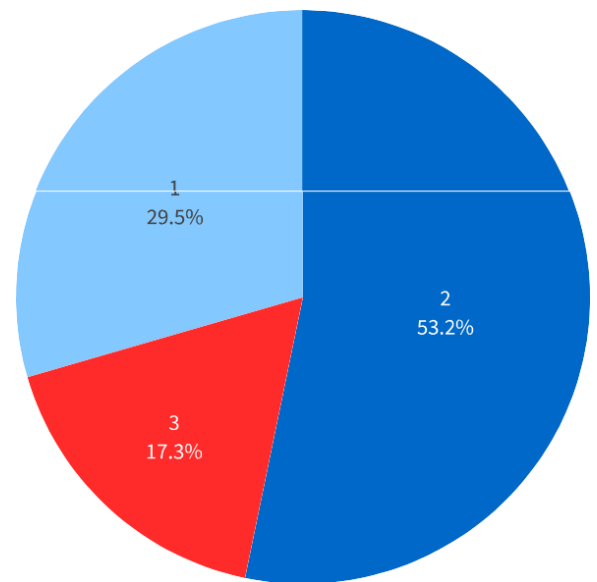
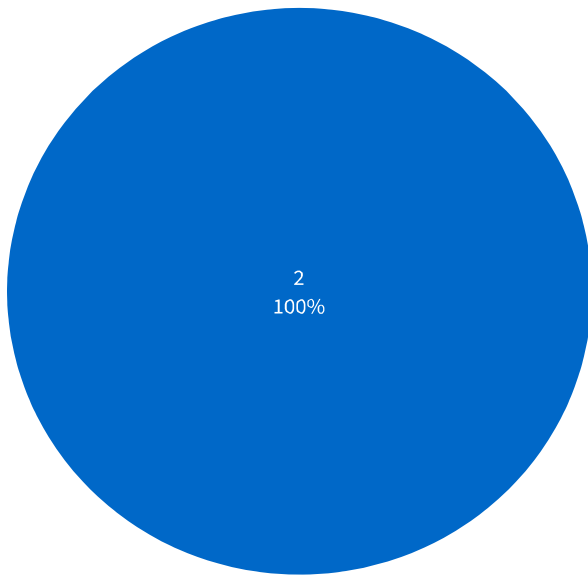
Higher Tidal Volume Ventilation (non-LPV)

A bar graph shows the number of deaths in each group:

- LPV Group: 21 deaths
- Non-LPV Group: 21 deaths

Each group had the same number of deaths (n=21) out of 139 total patients, indicating an equal mortality distribution between both ventilatory strategies.

ECMO Utilization



Pulmonary Vasodilators

Chapter 5

DISCUSSION

The correlation heat map highlights several clinically significant relationships. ICU LOS and Hospital LOS have a very strong correlation ($r = 0.84$), indicating that longer ICU stays greatly influence overall hospitalization duration. Initial PEEP, initial FiO_2 , and plateau pressure (Pplat) show moderate to strong intercorrelations, reflecting typical ventilator management where higher PEEP and plateau pressures often require increased FiO_2 to maintain oxygenation. The P/F ratio, a measure of oxygenation efficiency, negatively correlates with both SOFA and APACHE-II scores, indicating that worse organ dysfunction and higher illness severity are associated with poorer oxygenation. This inverse relationship suggests that worsening oxygenation (low P/F ratio) is associated with greater illness severity. The SOFA score, a marker of multi-organ failure, is positively correlated with ICU LOS and Hospital LOS, implying that higher organ dysfunction is associated with prolonged hospitalizations. Age negatively correlates with VFD ($r = -0.25$), indicating that older patients tend to spend more time on mechanical ventilation or experience worse outcomes. Some variables, such as Respiratory Rate, show low correlations with most other variables, indicating limited direct association in this dataset.

The data indicates that, although lung-protective ventilation (low tidal volume) was applied in most cases, a notable number of patients still received higher tidal volumes. Patients on lung-protective ventilation experienced better outcomes, including more ventilator-free days and shorter ICU and hospital stays. However, there was no statistically significant difference in mortality between the groups, likely influenced by factors such as comorbidities or illness severity. Adherence to plateau pressure and PEEP guidelines shows a clear effort to minimize ventilator-induced lung injury. Correlation analysis confirms expected physiological relationships, such as PEEP- FiO_2 and ICU-Hospital LOS, while also highlighting that outcomes like oxygenation and survival are influenced by multiple factors beyond ventilation settings.

The data confirms the use of lung-protective ventilation in many patients, a key recommendation in ARDS management. Despite some patients still receiving higher tidal volumes, those on LPV showed clinically better outcomes: they had more ventilator-free days and shorter ICU and hospital stays. Interestingly, while LPV improved morbidity-related outcomes, mortality rates did not significantly differ between the LPV and higher-volume groups. This could reflect multifactorial contributors to mortality in ARDS (e.g., comorbidities, severity of

illness, age) that extend beyond ventilator strategy alone. The strong correlation between ICU and hospital length of stay is expected and logical, as ICU duration significantly contributes to total hospitalization time. Likewise, correlations between ventilator parameters (PEEP-Foil₂ and TV-Pplat) align with clinical physiology and ARDS protocol- based ventilator adjustments.

The findings highlight clear benefits of lung-protective ventilation (LPV) compared to higher tidal volume strategies. Ventilator-free days (VFD) were significantly higher in the LPV group, suggesting faster weaning from mechanical ventilation and a lower risk of ventilator-associated complications. Both ICU and hospital lengths of stay were shorter for patients receiving LPV, indicating earlier recovery, fewer complications, and more efficient use of healthcare resources. The bar graphs show a consistent downward trend in LOS for the LPV group, reinforcing the advantages of following guideline-based ventilation strategies. These differences, although not explicitly labeled with p-values in the chart, appear clinically meaningful. They support existing evidence from ARDSnet trials and similar studies which promote LPV (typically ≤ 6 mL/kg predicted body weight) to reduce lung injury. Non-LPV patients showed longer mechanical ventilation duration and prolonged hospitalization, which may be attributed to polytrauma, barotrauma, and systemic inflammation triggered by higher tidal volumes.

This figure highlights a critical insight: ventilation strategy did not appear to affect mortality in this cohort. Despite evidence from previous ARDS trials suggesting a mortality benefit of LPV, this dataset shows: Equal number of deaths in both the LPV and non-LPV groups (21 patients each). This may indicate that factors other than ventilation strategies such as comorbidities, baseline disease severity, age, or timing of intervention—could have played a stronger role in determining outcomes. It also underscores the complexity of ARDS management, where multiple variables affect prognosis beyond ventilator settings alone. This finding contrasts with some studies that report lower mortality with LPV, but it aligns with real-world ICU data where strict protocol adherence may vary, and patient heterogeneity dilutes the measurable effect of one intervention.

Chapter 6

CONCLUSION

The correlation matrix provides valuable insight into the inter-relationships between clinical characteristics of patients in critical condition. The therapeutic importance of ICU resource usage is further supported by the substantial positive association between ICU and hospital duration of stay. Ventilator settings such as PEEP, FiO₂, and plateau pressure are closely interrelated and are significantly associated with oxygenation (P_f ratio), which reflects lung function. Markers of disease severity, particularly the SOFA and Apache II scores, demonstrate negative correlations with oxygenation indices and positive associations with hospitalization duration, underscoring their predictive utility. These findings help in understanding the dynamics between ventilatory parameters, severity scores, and patient outcomes, and can inform future clinical decision-making and research directions.

This analysis highlights the benefits of lung-protective ventilation (LPV) in reducing ICU and hospital burden, even though its impact on mortality is less pronounced. It emphasizes the importance of strict adherence to ARDS guidelines, particularly in managing ventilator settings. Future research should focus on long-term functional outcomes and identifying predictors of survival beyond ventilation strategies. Overall, the study shows that LPV improves key clinical outcomes, including ventilator-free days and shorter ICU and hospital stays. While mortality differences were not statistically significant, this underscores the need for holistic management beyond ventilator settings alone. Most patients met criteria for moderate ARDS, and ventilator parameters largely adhered to international safety thresholds. Correlation analysis confirms strong internal consistency and physiologically sound relationships among the measured variables.

These findings support continued adherence to LPV protocols and prompt further research into non-ventilatory factors affecting mortality in ARDS. Lung-protective ventilation enhances clinical outcomes for ARDS patients, as demonstrated by this analysis: Increases the number of ventilator-free days; Shortens hospital and ICU stays; Indicates a better overall recovery trajectory. Although mortality differences are not discussed in this specific figure, the trends in VFD and LOS provide strong support for the routine implementation of lung-protective strategies. The results highlight the significance of following evidence-based ventilator settings in improving both patient outcomes and system-level efficiencies.

The analysis of mortality outcomes shows: No difference in death count between patients managed with lung-protective versus higher tidal volume ventilation. While LPV showed benefits in other outcomes, mortality was unaffected in this sample. This suggests that LPV may improve morbidity but not necessarily survival, at least within the observed parameters of this study. These results emphasize the importance of comprehensive, multimodal care for ARDS patients and the need for further research into individualized treatment factors beyond ventilation strategies.

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APPENDICES

Appendix-1

ENGLISH CONSENT FORM

The study you are about to participate is a randomized control trial survey titled as; “Lung Protective Ventilation Strategies for Acute Respiratory Distress Syndrome (ARDS) Patients in ICU”. The study has no potential harm to participants. All data collected from you will be coded in order to protect your identity, and should not be disclosed to anyone. Following the study there will be no way to connect your name with your data. Your answers to the questions will not affect the quality of education given to you. Any additional information about the study results will be provided to you at its conclusion, upon your request.

You are free to withdraw from the study at any time. You agree to participate, indicating that you have read and understood the nature of the study, and that all your inquiries concerning the activities have been answered to your satisfaction.

NAME _____

SIGNATURE_____

DATE_____

Appendix-2

URDU CONSENT FORM

میں _____ تصدیق کرتا/ کرتی ہوں کہ محترمہ (YOUR NAME IN URDU) نے اپنی اس تحقیق

“Lung Protective Ventilation Strategies for Acute Respiratory Distress Syndrome (ARDS) Patients in ICU”

زیرنگرانی (YOUR SUPERVISOR NAME) کے متعلق بتا دیا ہے۔ مجھے اس تحقیق کی

نوعیت، مقاصد، احداث، توقعات، فوائد اور خطرات کے متعلق ، ساری معلومات فراہم کر دی گئی ہیں اس تحقیق کے دوران ساری معلومات صیغہ راز میں رہیں گی اور مریض کا نام اور دیگر معلومات صرف تحقیق کے لیے استعمال ہوں گی۔ مجھے یہ بھی بتا دیا گیا ہے کہ میں اس تحقیق سے متعلق ہر قسم کے سوال پوچھنے کا مجاز ہوں اور یہ تحقیق صرف ایک شخص ک مفاد میں نہیں ہے بلکہ بحسبیت مجموعی انسانیت کا مفاد اس سے وابستہ ہے۔ تمام تفصیلات جاننے کے بعد یس تحقیق میں شامل ہونے یا نہ ہونے پر کسی کا قائل نہیں ہوں۔ اس تحقیق سے کسی بھی وقت علیحدہ ہونے پر مجھ پر کوئی پابندی نہیں ہو گی۔ میں بذات خود بقائمی حوش و حواس

اور رضا مندی سے اس تحقیقاتی عمل میں شامل ہوتی/ ہوتا ہوں

دستخط محقق _____

دستخط شرکت کار _____

تاریخ _____

Appendix-3

QUESTIONNAIRES

Section 1: Demographic and Clinical Data

1. Patient ID (optional): ____
2. Age: ____ years
3. Gender: ☐ Male ☐ Female ☐ Other
4. Date of ICU admission: __/__/__
5. Primary diagnosis leading to ICU admission: _____
6. Comorbidities (check all that apply):
☐ COPD ☐ Diabetes mellitus ☐ Hypertension ☐ Chronic kidney disease
☐ Heart failure ☐ Immunosuppression ☐ None ☐ Other: _____
7. Severity scores:
 - APACHE II score on admission: ____
 - SOFA score on admission: ____
8. ARDS diagnosis (Berlin criteria):
 - Onset within 7 days of known insult: ☐ Yes ☐ No
 - Bilateral opacities on imaging: ☐ Yes ☐ No
 - Respiratory failure not fully explained by cardiac failure: ☐ Yes ☐ No
 - PaO₂/FiO₂ ratio at diagnosis: ____ (e.g., ≤300, ≤200, ≤100 for mild/moderate/severe ARDS)

Section 2: Ventilator Settings and Strategies

9. Initial ventilation mode:
☐ Volume-controlled ☐ Pressure-controlled ☐ Other: _____
10. Tidal volume (V_t):
 - Set V_t: ____ ml/kg predicted body weight (PBW)
 - PBW calculation method:
☐ Actual body weight ☐ ARDSnet formula (Male: $50 + 0.91[\text{height (cm)} - 152.4]$;
Female: $45.5 + 0.91[\text{height (cm)} - 152.4]$)

11. Plateau pressure (Pplat):

- Measured Pplat: ___ cmH₂O
- Is Pplat maintained ≤ 30 cmH₂O? ☐ Yes ☐ No

12. PEEP strategy:

- Initial PEEP level: ___ cmH₂O
- Titration method:
 - ☐ ARDSnet PEEP/FiO₂ table ☐ Esophageal pressure-guided ☐

Oxygenation/compliance-driven ☐ Other: _____

13. FiO₂ and PEEP adjustments:

- FiO₂ at initiation: ___%
- Frequency of FiO₂/PEEP adjustments: ☐ Hourly ☐ Every 4–6 hrs ☐ Daily ☐ Other:

14. Respiratory rate:

- Set rate: ___ breaths/min
- pH target: ___ (e.g., ≥ 7.25)

15. Permissive hypercapnia:

- ☐ Allowed ☐ Not allowed
- Highest tolerated PaCO₂: ___ mmHg

16. Recruitment maneuvers:

- ☐ Used ☐ Not used
- Method: ☐ Sustained inflation ☐ Incremental PEEP ☐ Other: _____
- Frequency: _____

Section 3: Adjunctive Therapies

17. Prone positioning:

- ☐ Used ☐ Not used
- Total sessions: _____
- Average duration per session: _____ hours

18. Neuromuscular blockade (NMB):

- ☐ Used ☐ Not used

- Agent: ☐ Cisatracurium ☐ Rocuronium ☐ Other: ____

- Duration: ____ days

19. Inhaled pulmonary vasodilators:

☐ Nitric oxide ☐ Prostacyclin ☐ Not used

20. Systemic corticosteroids:

☐ Used ☐ Not used

- Agent/dose: ____

21. ECMO:

☐ Used ☐ Not used

- Criteria for initiation: ____

- Duration: ____ days

Section 4: Monitoring and Adjustments

22. Arterial blood gas (ABG) frequency:

☐ Every 1–2 hrs ☐ Every 4–6 hrs ☐ Daily ☐ Other: ____

23. Parameters monitored (check all that apply):

☐ Dynamic compliance ☐ Driving pressure (Pplat – PEEP) ☐ SpO₂ ☐ Hemodynamics (CVP, MAP)

24. Hemodynamic monitoring tools:

☐ Central venous catheter ☐ Pulse contour analysis (PiCCO) ☐ Echocardiography ☐

None

25. Protocol for ventilator adjustments:

☐ ARDSnet protocol ☐ Institutional protocol ☐ Clinician discretion

Section 5: Outcomes

26. Ventilator-free days (days without mechanical ventilation in first 28 days): ____

27. ICU length of stay (LOS): ____ days

28. Hospital LOS: ____ days

29. Mortality: ☐ ICU mortality ☐ 28-day mortality ☐ Hospital mortality

30. Complications (check all that apply):

☐ Barotrauma (pneumothorax) ☐ Ventilator-associated pneumonia (VAP) ☐ AKI

requiring dialysis ☐ Pressure ulcers

31. Are you familiar with ARDSnet protocols? ☐ Yes ☐ No

Signature of Data Collector: _____

Date: _____

Appendix-4

PERMISSION LETTER

To

The Medical Director
Mufti Mehmood Memorial Teaching Hospital
Dera Ismail Khan, Khyber Pakhtunkhwa

Subject: Request for Approval to Conduct Research Study in ICU

Respected Sir,

I am writing to respectfully seek your kind permission to conduct a research study titled "**LUNG PROTECTIVE VENTILATION STRATEGIES FOR ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS) PATIENTS IN ICU**" at the Intensive Care Unit (ICU) of Mufti Mehmood Memorial Teaching Hospital, Dera Ismail Khan.

This study is a **cross-sectional observational research**, conducted under the Faculty of Allied Health Sciences, Superior University Lahore. The study aims to evaluate the effectiveness of respiratory strategies in early detection of respiratory failure among critically ill ICU patients. A total sample size of 139 patients will be enrolled over a four-month period using a convenience sampling technique.

The study will include adult ICU patients (18 years and above) who are critically ill and require continuous respiratory monitoring due to conditions such as sepsis, pneumonia, ARDS, or post-surgical complications. Patients not requiring intensive care, those with neuromuscular respiratory disorders, pregnant patients (if ethically required), patients with incomplete medical records, and those already on long-term ventilation prior to ICU admission will be excluded.

All ethical considerations will be strictly followed. Informed consent will be obtained from patients or their legal guardians prior to data collection. Patient confidentiality and privacy will be maintained, and no personal identifiers will be disclosed. Data will be collected through structured data sheets and analyzed using SPSS version 22, applying descriptive statistical methods. Findings will be presented in the form of tables, graphs, and text.

This research is expected to contribute significantly to improving ventilatory strategies, optimizing ventilatory decisions, reducing ICU complications, and enhancing patient outcomes.

I assure you that this study will not interfere with routine patient care and will be conducted in full compliance with hospital policies and ethical standards. I kindly request your approval to carry out this research at your esteemed institution.

I shall be highly grateful for your cooperation and support.

Allowed
Fahad

Yours sincerely,
ASIF AHMAD

Appendix-5

ETHICS COMMITTEE LETTER



OFFICE OF THE DEAN-FAHS

SUPERIOR UNIVERSITY

Ref.: IRB /FAHS/Allied/04/25/MS/AHS-3761

Date: 18th March 2025

Program: MS Allied Health Sciences

Name: Asif Ahmad

Registration: SU91-MSAHW-F23-025

Subject: Ethical Approval Letter

The Research Ethical Committee convened on Dated: **17th March, 2025** to discuss your protocol titled "**Lung protective ventilation strategies for acute respiratory distress syndrome patients in ICU**"

No further corrections and recommendations were suggested. The above-mentioned protocol has been approved after considering various research issues including ethical concerns with condition that the researcher will submit completion report at the end of his/her research.

Prof. Dr. Muhammad Naveed Babur
Dean/Convener REC
Faculty of Allied Health Sciences
Superior University, Lahore

Appendix-6

PLAGIARISM SI CERTIFICATE

April 13, 2026



PLAGIARISM CERTIFICATE

For MPhil and PhD

This is certified that the thesis entitled: **Lung Protective Ventilation Strategies For Acute Respiratory Distress Syndrome (ARDS) Patients In ICU.**

Student Name: Asif Ahmad

Reg /Roll No: SU91-MSAHW-F23-021

Submitted on date: 13.04.2026

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Appendix-7

PLAGIARISM REPORT



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