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Prone Positioning: A Comparison Between COVID-19 ARDS and non-COVID-19 ARDS

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Doctor of Nursing Practice

by

Albert Ji Chul Shin

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ABSTRACT OF THE DISSERTATION

Prone Positioning: A Comparison Between COVID-19 ARDS and non-COVID-19 ARDS

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Albert Ji Chul Shin

Doctor of Nursing Practice

University of California, Los Angeles

Professor Dong Sung An, Chair

Background: Coronavirus disease 2019 (COVID-19) is a viral respiratory disease caused by SARS-CoV-2. Critical cases evolve into an acute respiratory distress syndrome (ARDS) with bilateral infiltrates, intrapulmonary shunting, and hypoxemia requiring intubation. A rescue treatment called prone positioning has been frequently utilized during the pandemic and known to improve dorsal lung ventilation, decreasing shunting, and improving mortality rates in non-COVID-19 ARDS literature. The clinical inquiry is whether a resource intensive procedure like pronation can benefit oxygenation, ICU length of stay, and days intubated in COVID-19 ARDS. **Objective:** To evaluate the effects of pronation and compare COVID-19 ARDS with a historical control group of non-COVID-19 ARDS. The specific aim is to assess whether there is a positive effect on oxygenation, ICU LOS, and days intubated. **Methods:** A retrospective descriptive chart review of COVID-19 ARDS versus non-COVID-19 ARDS adult patients ages 18 to 80 years at a quaternary academic center in Los Angeles, California. A convenient sample of intubated

COVID-19 patients with moderate to severe ARDS based on the Berlin criteria. A historical control was age and gender matched of non-COVID-19 ARDS patients. Statistical analysis utilized Mann Whitney U, and the Wilcoxon Signed Rank Test. **Results:** A total of 41 patients met criteria in the COVID-19 ARDS group, and six patients in the non-COVID-19 ARDS group for a total sample size of 47 subjects. Pronation showed a positive impact on oxygenation (P/F ratios) at the end of pronation on day one ($p < 0.01$), day three ($p < .042$), and day four ($p < 0.04$) in the COVID-19 ARDS group compared to the non-COVID-19 ARDS group. The Wilcoxon Signed Rank Test found a positive impact on P/F ratios by pronation from day one through day six in the COVID-19 ARDS group while the non-COVID-19 group showed a positive impact on day two.

Conclusion: Pronation impacted P/F ratios in COVID-19 ARDS compared to non-COVID-19 ARDS. ICU LOS and intubation days were not impacted by pronation. Oxygenation improvement was possibly related to assertive prone protocols instituted early during the exudative phase of ARDS. These results suggest there is an oxygenation benefit to pronating early.

The dissertation of Albert Ji Chul Shin is approved.

Anna F. Gawlinski

Carol L. Pavlish

Nancy A. Pike

Dong Sung An, Committee Chair

University of California, Los Angeles

2021

Dedication

This dissertation is dedicated to my mother Hee Cha, and father Hyun Chul Shin. My parents were first generation Korean Americans who immigrated to the U.S. to pursue the American dream and had provided a better life for their family. My mother had a successful career as a RN at a hospital in Los Angeles for over 40 years. This project is in honor of my working-class grandparents who did not have the opportunities of a college education and survived through the Imperial Japanese occupation in Korea from 1910-1945, and the Korean War. My paternal grandfather, Myung Kyun Shin, was an infantryman as a mortar specialist for frontline warfare during the Korean War and eventually transitioned as a South Korean army reconnaissance aircraft mechanic. He immigrated to the U.S. where he had a successful career as a machinist. My maternal grandfather, Moon Dong Park, was a carpenter who escaped the North Korean army troops as a prisoner of war for skilled laborers and survived with the help of some friendly people along the way making his way back to his family and newborn daughter, my mother. He had a successful carpentry business for over 60 years and enjoyed producing quality craftsmanship for the community. Through their hard work, sacrifice, prayers, and strong proponent of education, this doctorate degree in nursing practice was possible.

"The mindset isn't about seeking a result – it's more about the process of getting to that result. It's about the journey and the approach. It's a way of life. I do think that it's important, in all endeavors, to have that mentality." Kobe Bryant

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To the Chair of the UCLA DNP program, Dr. Nancy Bush. Thank you for your mentorship and encouragement. Thanks for coaching us with exemplary leadership and skill through this program. I have learned tremendously from you and the nursing faculty at UCLA. Your compassion and leadership especially during the height of the pandemic steered our cohort and my doctoral journey at UCLA to success. Special thanks to Soo Kwon and her expertise who was also pivotal in making my experience at UCLA nursing exemplary especially during the COVID-19 pandemic. Thank you to the UCLA DNP class of 2021. It has been a privilege to learn from you. Go Bruins!

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To my family and friends, thank you so much for your support, words of encouragement, and prayers to see me progress throughout my nursing career. It has been a great journey and I have been blessed to have this opportunity to serve people through the art and science of nursing. All glory to our Father in heaven. May God continue to guide me in this profession to advance nursing practice and to help people to the best of my ability.

VITA

Albert J. Shin, MSN, NP, AGACNP-BC, CCRN

EDUCATION

Master of Science in Nursing – Adult-Gerontology Acute Care Nurse Practitioner
California State University, Los Angeles 2019
Los Angeles, CA

Bachelor of Science in Nursing
California State University, Fullerton 2016
Fullerton, CA

Associate Degree in Nursing 2010
Santa Barbara City College, Santa Barbara Santa Barbara, CA

LICENSURE / CERTIFICATION
State of California Nurse Practitioner (APRN): NP 95012670. Expires: 9/30/22
State of California Furnishing: 95012670. Expires: 9/30/22
State of California Professional Nurse License (RN): RN 792313 Expires: 9/30/22
ACLS Expires: 6/01/24
BLS Expires: 6/01/24
NIHSS Expires: 6/01/24

BOARD CERTIFICATION
Adult-Gerontology Acute Care NP (AGACNP-BC): #2019014407 Expires: 7/02/24
American Nurses Credentialing Center

Acute/Critical Care (CCRN): #2000086228 Expires: 6/30/24
American Association of Critical Care Nurses

WORK EXPERIENCE
Critical Care Nurse Practitioner, **Good Samaritan Hospital,** Los Angeles, CA 3/2020 – Present

- Provide critical care services in an adult 12 bed CVICU and 24 bed MICU.
- Critical care diagnostics, drug therapeutics, assessment and plan, family meetings.
- History and physicals, progress notes, comprehensive system-based plans, consult specialists.
- Manage code blue, rapid response, code stroke teams, and end of life care discussions.
- ABG analysis, mechanical ventilation management, chest x ray, COVID-19 management, EKG analysis and therapeutics.

Critical Care Registered Nurse, **USC Verdugo Hills Hospital,** Glendale, CA 6/2016 – 2/2020

- Started as a telemetry nurse and transitioned to critical care in 2017. Critical care course and training completed in 8/2017 and achieved board certification (CCRN) in July 2018.
- Rapid response, and code blue teams. IV start team.
- Titration of critical care IV drips.
- EKG analysis and therapeutics.

Registered Nurse, **Pro Care One,** Anaheim, CA 8/2014 – 04/2020

- Provided nursing services in telemetry at Citrus Valley Hospitals from 2014 to 2019. Transitioned to critical care units at Citrus Valley Hospitals from 2018 to 2020.
- Experienced with telemetry rhythm analysis and therapeutics.

Registered Nurse, **Carrillo Surgery Center,** Santa Barbara, CA 6/2013 – 12/2015

- Circulating nurse, pre / post op care provided at an outpatient surgery center.

LVN to Registered Nurse, **Cottage Health System,** Santa Barbara, CA 7/2008 – 8/2013

- Subacute vocational nurse in 2008-2011. Transitioned to RN residency program in acute care orthopedics in 2011 with successful completion of training and 2-year work commitment.

PROFESSIONAL ORGANIZATIONS / AWARDS

Sigma Theta Tau – Gamma Tau Chapter	2021 - present
DAISY Award – The DAISY Foundation. USC Verdugo Hills Hospital ICU	2018
American Association of Critical Care Nurses	2016 - present
Wound Care Committee – Cottage Health System	2012 – 2013
Calm, Considerate, and Compassionate Care Committee – Cottage Health System	2010 - 2011

SCHOLARLY WORK

Author, **DNP Project, Chair Dr. Dong Sung An** 2021

“Prone positioning: A comparison between COVID-19 ARDS and non-COVID-19 ARDS.”

COMMUNITY SERVICE

Doctors Without Walls, RN volunteer Santa Barbara, CA 11/2012 – 5/2013

Chapter One: Introduction

The *Coronavirus Disease* 2019 (COVID-19) has been one of the deadliest pandemics in human history since the 1918 Influenza pandemic (H1N1 virus) with 251,885,689 confirmed cases and 5,079,013 global deaths. In the United States, there are 46,847,655 confirmed cases and 759,636 reported deaths, as of November 11th, 2021 (Johns Hopkins University & Medicine [JHU], 2020). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a newly emerged coronavirus that causes COVID-19 disease. SARS-CoV-2 infect lung epithelial cells through host cell angiotensin converting enzyme II (ACE2) receptor in lungs. SARS-CoV-2 causes a cytokine storm by invoking neutrophilia, diffuse pulmonary infiltrates, vascular fluid accumulation, shunting, and subsequent hypoxemia. COVID-19 invokes mild versus severe symptoms with the latter being associated with critical disease and the potential for rapid decompensation related to acute respiratory distress syndrome (ARDS), and multi-organ system injury. According to the Centers for Disease and Prevention (CDC), mortality rates in the Intensive Care Unit (ICU) range from 39% to 72% with a median length of hospitalization in survivors at 10-13 days (CDC, 2021). This is the third coronavirus after the SARS-CoV from 2002 and the Middle East respiratory syndrome (MERS) of 2012 that are known to affect humans and cause serious respiratory disease and fatalities (National Institute of Allergy and Infectious Diseases [NIAID] 2020).

Theoretically, COVID-19 may have originated from zoonotic origins (i.e., bats, cats, camels) and usually infect animals (Los Angeles County Department of Public Health, 2020). COVID-19 is transmitted through respiratory droplets and causes a viral pneumonia. Researchers have found that COVID-19 causes viral pneumonia through confirmation of a rhesus macaque model where high viral loads were detected from the nose, throat, and rectum (NIAID, 2020).

Histological analysis found pulmonary disease processes of pneumonia with infiltration of lymphocytes, macrophages, neutrophils, thickening of alveolar tissue, and increased lung weight (Munster et al., 2020). SARS-CoV-2 is caused by a single strand RNA virus surrounded with a lipid bilayer membrane of virus spike proteins. The virus spike proteins mediate entry via binding to the angiotensin-converting enzyme II (ACE2) receptor to infect the epithelial layer of alveoli cells of the lungs. The virus infection affects multiple organs that express the ACE2 receptor including the gastrointestinal tract, heart, and kidneys (NIAID, 2020; Levy & Sanchez, 2020).

Severe COVID-19 causes dyspnea and hypoxemia with impending respiratory failure after the initial onset of symptoms (Berlin et al., 2020). The criteria of severe COVID-19 include dyspnea, respiratory rate of greater than 30 breaths per minute, oxygen saturation of 93% or less, partial pressure of arterial oxygen (PaO_2) and fraction of inspired oxygen (FiO_2) (P/F ratio) of less than 300 mm Hg, or infiltrates on more than 50% of the lungs in 24 to 48 hours of the onset of symptoms (Berlin et al., 2020). Eighty one percent of COVID-19 cases have mild to moderate, 14% of patients have severe symptoms including dyspnea, pneumonia of more than 50% on diagnostic imaging like chest x-ray or chest computed tomography (CT) images, and critical symptoms such as respiratory failure, shock secondary to viral pneumonia, and multi-organ dysfunction (CDC, 2020; Levy & Sanchez, 2020;). As a result of multi-organ failure, severe COVID-19 patients in the ICU had high mortality rates. The high mortality rates were associated with an acute lung injury as known as acute respiratory distress syndrome (ARDS).

In 72 hospitals in Italy during Europe's first COVID-19 surge, the median ICU length of stay (LOS) of discharged patients was eight days, and seven days of ICU LOS for those who expired. The mortality rate was 26% in the ICU (Grasselli et al., 2020). In 12 hospitals in New

York City, mechanically ventilated patients with COVID-19 were discharged at 3.3% (n=38) and 24.5% (n=282) expired (Richardson et al., 2020). Mortality rates for ventilated patients for ages 18 to 65 years were 76.4% compared to 97.2% for ages > 65 years (Richardson et al., 2020). The mortality rate in the Lombardy region of Northern Italy was 48.8% in the ICU and 53.4% in the hospital (Grasselli et al., 2020). In China at Tongji hospital, mortality rates were reported at 88.3% in patients with COVID-19 ARDS (Wang et al., 2020). In COVID-19 ARDS cases admitted to the ICU in Wuhan, China, mortality rates ranged from 67 to 85% (CDC, 2020).

Neutrophils are a dominant white blood cell in the peripheral blood and lungs in SARS-CoV and MERS with worsening lung damage associated with diffuse pulmonary infiltrates of neutrophils and macrophages in peripheral blood samples (Wu et al., 2020). In Wuhan, China, patients with COVID-19 ARDS had neutrophilia at higher levels compared to patients without ARDS and a presumable cytokine storm. A localized systemic inflammatory state causes an innate and adaptive immune response damaging the endothelial layer of pulmonary capillaries, increasing bilateral interstitial edema, and causing lung injury known as acute respiratory distress syndrome (ARDS). The ARDS state increases intra-alveolar fibrin formation due to cellular debris from pulmonary injury and an activation of the coagulation system (Grasselli et al., 2020). The physiological process of ARDS increased mortality risk with decreased lung compliance and elevated D-dimers (i.e. a serum laboratory marker frequently utilized during COVID-19 to evaluate vascular injury due to COVID-19) (Grasselli et al., 2020). The 28-day mortality rate was greater with patients with high d-dimers and low compliance at 56% compared to 27 % of low d-dimers and high compliance. This was supported by quantitative analyses of computed tomography (CT) scans of the lungs that showed associated decreased perfusion as a result of increased hypercoagulability burden from the pulmonary injury. There was a similarity in static lung compliance and lung weight with decreased lung compliance, high variability of mechanical ventilation, and decreased alveoli recruitment with COVID-19 ARDS compared to non-COVID-19 ARDS (Grasselli et al., 2020).

ARDS

ARDS is a respiratory disease characterized by acute lung injury related to an acute inflammatory process that involves fluid accumulation in the pulmonary vascular space and decreased alveolar perfusion (Bellani et al., 2016). The risk factors for ARDS include direct and indirect lung injury risks. Direct lung injury risks include pneumonia (e.g., influenza viruses, SARS-CoV-2, or MERS), aspiration, pulmonary contusion, and inhalation injury. Indirect lung injury risks include sepsis, trauma, hemorrhagic shock, pancreatitis, burn injuries, drug overdose, transfusion of blood products, cardiopulmonary bypass surgery, and reperfusion edema post lung transplantation (Thompson et al., 2017). Most common causes of ARDS are from pneumonia or sepsis. ARDS occurs within seven days after a clinical diagnosis of sepsis or pneumonia with an age adjusted occurrence of 86.2 cases per 100,000 reported in the US (Rubenfeld et al., 2005). Genetic factors may have a role in the susceptibility of ARDS with particular attention to the angiotensin converting enzyme (ACE) and the coronavirus. Specifically, the ACE2 protein is a receptor for the SARS-CoV.

There are three phases of ARDS: early exudative, fibroproliferative, and fibrotic. The early exudative phase is the initial stage of lung injury that begins in the first seven to ten days. This stage is characterized by interstitial fluid accumulation, hyperplasia of type II pneumocytes, and hyaline membrane formation through activation of the cellular immune response. Cytokines are released by macrophages propagating an inflammatory cascade and causes a sustained tissue injury to the endothelial and epithelium. The early exudative phase occurs in the first seven to ten days and the fibroproliferative phase is associated with prolonged ventilation due to fibrotic lung injury (Siegel et al., 2021). Histological reports have shown diffuse interstitial fibrosis within the proliferative stage (Katzenstein et al., 1986). The fibroproliferative phase can also lead to compensational failure due to the adaptive immune response and reduced pulmonary compliance due to the propagated inflammatory state. This leads to worsening gas exchange, increased partial pressure of arterial carbon dioxide ($PaCO_2$), and ventilation / perfusion (V/Q) mismatch (Smith & Shifrin, 2021). This phase occurs from seven to ten days of ARDS and may extend two to three weeks (Siegel et al., 2021). Patients who survive the fibroproliferative phase can potentially transition into a repair phase where lung injury slowly improves overtime from weeks to months (Siegel et al., 2021). The fibrotic stage occurs where there is complete damage to the epithelial surface with a failure to re-epithelialize. Myofibroblasts are formed with an abundance of fibroblasts and intra-alveolar fibrosis. This stage is associated with prolonged mechanical ventilation and mortality (Siegel et al., 2021).

The Berlin Definition of ARDS from Bellani et al. (2016) was developed by a landmark cooperative of *The ARDS Definition Task Force* that re-defined the classification based on an improved predictive value of mortality. The Berlin criteria of ARDS is classified as mild, moderate, and severe. Analysis of the clinical database found a parallel ascending mortality risk with mild to severe ARDS (i.e. 20%, 41%, 52%, mortality risk respectively). The Berlin Definition includes 1) PaO_2, 2) FiO_2, 3) P/F ratio, 4) positive end expiratory pressure (PEEP) ≥ 5 cm of water, 5) chest imaging criteria with bilateral opacities, and 6) respiratory failure that is not related to cardiac failure or fluid volume overload (Ranieri et al., 2012).

The Berlin Definition criteria excluded the use of a pulmonary artery catheter for wedge pressure measurements due to the decreased frequency of utilization, and fluid volume overload in the setting of cardiac failure that may be part of the physiological response of ARDS. Further ARDS criteria include the diagnosis respiratory failure that is not caused by heart failure or fluid volume overload. An objective assessment tool such as an echocardiogram would be necessary to rule out hydrostatic edema when no ARDS risk factor is present (Ranieri et al., 2012).

The American-European Consensus Conference (AECC) definition of ARDS was defined in 1994 which then had provided a greater expansion of knowledge, clinical, and epidemiological data. However, this was an imperfect criterion that struggled with specific inclusion criteria including ventilator setting, and chest radiographic imaging. Acute lung injury (ALI) was difficult to diagnose between both ALI and ARDS. ALI criteria were interpreted as a P/F ratio of 201 to 300 mmHg while ARDS was defined as a P/F ratio < 300 mmHg. In addition, the AECC did not take into consideration of PEEP that had impacted P/F ratios and was later introduced through the Berlin definition. The criteria were nevertheless important through the evolution of refining the complexity of ARDS.

Prone Positioning

Prone positioning optimizes ventilation of the dorsal regions in the lungs, reduces intrapulmonary shunting, and improves oxygenation. The scientific evidence showing the benefits of prone positioning is predominantly in non-COVID-19 ARDS and largely influenced by the landmark Proseva trial. This randomized controlled trial (RCT) utilized a manual process for their pronation protocol requiring multiple healthcare professionals to effectively turn a patient laterally from supine position to prone position utilizing a slide sheet method of two large bed sheets (Church & Chechile, 2020). Another method seldom utilized is the Rotoprone bed which is a special ICU bed designed for the purposes to automatically pronate a patient. This is facilitated with HCW to laterally rotate immobile patients automatically up to 62 degrees bilaterally in supine and prone positions ("RotoProne Therapy System," 2019).

Prone positioning also known as pronation is a nursing intervention in ARDS that helps recruit alveoli in dependent lung areas that are susceptible to alveolar collapse due to the pulmonary disease process, lung compliance, and weight of lungs (Vollman et al., 2017). The benefits include decreased thoracic pressure against the lungs, and greater aeration of lung parenchyma. During mechanical ventilation, abdominal structures cause pressure against the diaphragm that is normally a protector against abdominal content pressure in spontaneous breathing. However, due to sedation, paralyzing agents, positive pressure ventilator settings, the activity of the diaphragm muscle is dormant decreasing dependent lung volumes and functional residual capacity (FRC). Supine position in ventilated patients also provides increase pleural pressure and decreased compliance causing greater propensity of collapsed alveoli during end expiration. Lung weight from edema in ARDS causes decreased lung aeration and alveolar collapse in the dorsal lung regions. Increased distribution of FRC and tidal volume uniformity occurs with pronation causing increased oxygenation by greater aeration of lung parenchyma (Vollman et al., 2017).

Additional interventions to be considered during prone positioning include: 1) educating the patient and family to decrease anxiety and provide sedation for Richmond Agitation Sedation Score (RASS) of -4 to -5; 2) use of enteral feeding including the use of prokinetics or post pyloric feedings to prevent aspiration from vomitus, and to provide reverse Trendelenburg position to reduce micro-aspiration risk; 3) pressure ulcer prevention including assessing for areas common for skin breakdown in prone position and the use of hydrocolloid dressings over chest, pelvis, elbows, knees, face, and placement of headpiece; 4) application of electrocardiogram (ECG) leads from anterior to posterior chest wall; 5) ensure proper eye care with lubrication and taping eye lids horizontally; 6) assess tongue to prevent potential tongue breakdown from teeth or use of a bite block; 7) tape endotracheal tube ties with tape and wrap around the head for extra support as saliva can loosen ties; 8) avoiding use of endotracheal tube (ETT) securement devices to prevent skin breakdown around face and cheeks. In addition, central, and arterial lines need to be sutured in place, and capnography monitoring is recommended for prone positioning and to assess for proper ETT positioning during turning procedure; 9) repositioning the patient's head hourly to prevent facial pressure ulcers (Vollman et al., 2017).

Pronation can also help mitigate ventilator-induced lung injury like barotrauma secondary to high utilization of PEEP with ARDS patients (Barakat-Johnson et al., 2020). The potential adverse effects with prone positioning are pressure ulcers as a RCT found statistical significance of pressure ulcer formation in prone versus supine groups at 13.92 and 7.72 per 1,000 ICU days with greatest incidences reported in the first seven days of pronation (Girard et al., 2014). Non-scheduled extubation was reported in 13.3% (n=31) of prone groups compared to 10.9% (n=25) in supine groups and were not statistically significant in a RCT of severe ARDS patients (Guerin et al., 2013). A cross sectional study of COVID-19 patients in Italy found bleeding to occur in the upper airways at 17.5%, medical device displacement at 12.7%, and only 6.8% of prone cycles that were interrupted (Binda et al., 2021). Pressure ulcers were not statistically significant and were not associated with prone frequency (Binda et al., 2021). Pronation during the pandemic in Italy was utilized 48% as rescue treatment. The most common area of pressure ulcers was on the ventral area of the body (i.e. chin, cheekbone) (Binda et al., 2021).

The current guidelines of prone positioning for non-COVID-19 ARDS based on the American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical-Care Medicine (ATS/ESICM/SCCM) is to pronate for > 12 hours per day (Fan et al., 2017). The standards for COVID-19 ARDS patients based on the SCCM is to pronate 12 to 16 hours per day for moderate to severe ARDS ("COVID-19 Resources," 2020). This recommendation is based on the *Surviving Sepsis Campaign* for critically ill patients with COVID-19 that found a mortality benefit in a meta-analysis of non- COVID-19 ARDS with pronation for at least 12 hours (Alhazzani et al., 2020). The American Association of Critical-Care Nurses (AACN) suggests non-COVID-19 ARDS pronation for 16 hours with a P/F ratio < 150 mmHg, FiO_2 > 60%, and PEEP of 5 cm of water (Vollman et al., 2017). The benefits of prone positioning are greater optimization of ventilation and aeration of lung parenchyma in the dorsal regions, reducing intrapulmonary shunting, decreases barotrauma, and translates to improved oxygenation and a mortality benefit.

Problem Statement

Current data on the efficacy of prone positioning in COVID-19 ARDS are lacking. Studies are limited to prospective, and cohort studies. The outcomes of pronation and how it impacts oxygenation (P/F ratios), ICU LOS, and intubation days in COVID-19 ARDS are unknown.

Prone positioning has increased physical and psychological demand of a health care team during this pandemic where non-ICU staff in one cohort study was utilized to optimize the safety of staff and patients for this intervention. Twelve percent of respondents reported pronation related anxiety, back and joint pain (Doussot et al., 2020). COVID-19 ARDS patients in the ICU are at high risk of increased ventilation days, multi-system organ failure and a complex hospitalization course with high mortality rates. Data on outcomes can improve the structure and process to minimize risk to patients and staff.

Background

Due to the lack of effective COVID-19 therapy with ARDS patients, prone positioning is a rescue treatment to improve oxygenation and hopeful recovery. The adverse effects associated with pronation are endotracheal tube dislodgement, optic disc edema, retinal hemorrhages, pressure ulcers to the face, chest, shoulders, knees, and risk of cardiac arrest in prone positioning (Hadaya & Benharash, 2020; Sun et al., 2020). Current research on outcomes of prone positioning and COVID-19 ARDS are limited and this project presents an opportunity to retrospectively evaluate pronation. A pandemic surge of severely critically ill COVID-19 ARDS can contribute to overwhelming a health care system related to limited resources such as nursing staff, protective equipment supplies, critical care beds, and ventilators (Berlin et al., 2020).

PICO Question

In adults 18 to 80 years with COVID-19 ARDS (P), how does prone positioning (I) compared to non-COVID-19 ARDS (C) impact oxygenation (P/F ratios), ICU LOS, and intubation days (O)?

Purpose and Objective

The purpose of this study is to compare pronation outcomes with COVID-19 ARDS and a historical non-COVID-19 ARDS control group. Details of prone positioning and outcomes would provide insight on an important ARDS treatment, improve patient safety, and help optimize future nursing protocols for COVID-19 ARDS in the adult ICU. This project can provide insight to re-building the structure and process of pronation protocols as the outcomes of pronation are not well known in COVID-19.

Chapter Two: Theoretical Framework

The theoretical framework for this Doctor of Nursing Practice (DNP) project is Donabedian's model: structure, process, and outcome (Donabedian, 1966). Donabedian's model takes into account the processes of what constitutes good medical care through rigorous analyses that consider values and standards (Donabedian, 1966). Structure is the setting where necessary tools are placed to deliver good care including hospital as a macrosystem and the Medical Intensive Care Unit (MICU) as a microsystem. Donabedian (1966) described process as an unbroken chain of means, followed by an intermediate end that proceeds towards the goal of health. This is the build and rebuild cycle of improving patient care within a microsystem. COVID-19 ARDS patients need optimized oxygenation and lung protective ventilation to improve overall survival in the ICU. Pronation process can be further re-evaluated to improve patient safety and outcomes. Outcome serves as the basis of validation. However, Donabedian (1966) considered a careful process of assessing both positives and negative outcomes and to consider whether good medical care is achieved. Thus, a comparative study can help evaluate whether current pronation protocols in this institution are effective.

The *structure* at the macrosystem includes hospital, medical management, and nursing administration. Medical planning includes COVID-19 pharmaceutical therapies for invasive mechanical ventilation like corticosteroids, and Tocilizumab (National Institutes of Health [NIH] 2021). Nursing administration includes assistance with labor intensive pronation teams and interprofessional collaboration with at least four health care workers including nursing assistants, license vocational nurses, and respiratory technicians. There is training and procedural protocols that also need pronation specific supportive infrastructure like pressure injury prevention surfaces (i.e. Stryker iso air mattress [Stryker Corporation, Kalamazoo, MI], Kreg EZ wider mattress [Kreg Therapeutics, Melrose Park, Il], Z-Flo fluidized positioner [Molnlycke Health Care, Peachtree Corners, GA], coloplast barrier sheet [Coloplast Corporation, Minneapolis, MN], and intravenous tubing extensions, feeding pumps, and additional sheets and pillows. Pronation can also be a challenge due to labor intensity demands during a pandemic surge as medical facilities have at times changed nursing ratios to 1:3 compared to 1:2. In New York City, ICU nursing ratios increased as high as 1:6 (Anderson et al., 2020). This can impact safe monitoring and implementation of the pronation procedure.

The *structure* at a microsystem includes the MICU, pronation protocol, staffing, and training. *Structure* helps address the pronation procedure as the problems with current practice is the inability to successfully liberate ARDS patients off invasive mechanical ventilation despite supportive treatments, and aggressive pronation protocols. Risks of complications and mortality incrementally increases due to further prolonged course of ventilation.

Process is the current nursing procedure for prone positioning implementation that involves decision making, expertise, and skill. Specific details that are not indicated in the protocol is criteria when to stop pronation as refractory hypoxemia in COVID-19 ARDS can have clinicians permissively prone greater than 24 hours per intervention cycle. Typically, pronation was stopped after P/F ratios were > 150 mmHg. However, when supinating patients back to supine position, there was worsening hypoxemia requiring immediate re-pronation. The protocol is ordered and discontinued by the intensivist medical group (i.e. physicians, nurse practitioners). The duration of pronation is 16 hours. The process of prone positioning is based on the AACN procedure manual for pronation therapy that was based on the standard set by the Proseva trial (Vollman et al, 2017; Guerin et al., 2013). The criteria for prone positioning includes a P/F ratio < 150 mm Hg, FiO_2 > 60%, and at least PEEP of 5 cm of water. The AACN procedure manual for discontinuation criteria of prone positioning includes: improvement of oxygenation in supine position for at least four hours with a P/F ratio $\geq$ 150 mm Hg with $FiO_2 \leq$ 60%, PEEP $\leq$ 10 cm of water, or a P/F ratio > 20% of the relative ratio in supine position (Vollman et al., 2017). The equipment needed for manual prone positioning are pillows, four to five healthcare workers, two flat sheets, and adjunct equipment like electrocardiogram and capnography monitors, and additional equipment as needed like pressure ulcer preventative pads (Vollman et al., 2017).

The MICU team on 4ICU at University of California Los Angeles (UCLA) Ronald Regan Health utilizes a prone positioning procedure similar to the Proseva trial. Theoretically, if oxygenation is improved and ventilatory requirements diminish, there can be an assertive process led by nurses and respiratory technicians to optimize sedation and ventilator requirements for ventilation weaning protocols.

The primary *outcome* will be the findings of this scholarly project specifically with the ratio of a partial pressure of arterial oxygen (PaO_2) to fraction of inspired oxygen ratio (FiO_2) (P/F ratio), positive end-expiratory pressure (PEEP), intubation days, ICU LOS. Outcomes of prone positioning can provide insight to recovery and how to improve the protocol.

Chapter Three: Review of the Literature

Search engines of PUBMED, CINAHL, and the clinical resource of UPTODATE were utilized. There were no RCTs for keywords “COVID-19 ARDS,” and “prone positioning.” For non-COVID-19 ARDS, keywords were “prone positioning,” and “ARDS,” search criteria included from the year 2000 to 2020 and RCTs. The inclusion criteria were prone positioning, intubation days, and ICU LOS. Exclusion criteria were studies that did not have prone positioning as the primary intervention of focus. The number of articles that that were identified in PUBMED were 29, and 474 on CINAHL. Six RCTs met inclusion criteria, and a prospective cohort study. One single center cohort study on COVID-19 ARDS, and one retrospective study on COVID-19 ARDS were included for literature review. There were no recent RCTs of adult prone positioning on intubated ARDS patients since 2013 with exception of two secondary studies from the Proseva trial measuring the impact of pronation on the development of pressure ulcers in 2014, and ventilator associated pneumonia in 2016. Excluded ARDS studies and RCTs that populated on the PUBMED search criteria not applicable to this project were the following: children, corticosteroids use in ARDS, driving pressures, post-surgical esophagectomy, pressure ulcers in ARDS, lung morphology versus PEEP, non-intubated patients, ventilator-associated pneumonia in ARDS, PEEP, and prone positioning in high altitudes. CINAHL search engine resulted in one RCT not specifically related to prone positioning and therefore excluded. Thus, this review yielded eight articles listed in Table # 2 (Table of Evidence).

Non-COVID-19 ARDS RCTs in the early 2000s found a positive effect on P/F ratios with daily prone positioning interventions in a ten day RCT ($p = 0.02$) compared to a seven day report of a positive oxygenation effect in another trial ($p < .001$) (Gattinoni et al., 2001; Guerin et al., 2004). The pronation duration in these RCTs averaged a mean (SD) 7 ± 1.8 hours compared to 8 hours (interquartile range, 7.7-9.8) (Gattinoni et al., 2001; Guerin et al., 2004). Mancebo et al. (2006) found a positive effect with pronation on day two with a mean (±SD) P/F ratio at 218 ± 85 in prone groups compared to 171 ± 85 in supine groups ($p = 0.002$), and day four with a P/F ratio of 215 ± 73 in prone compared to 176 ± 72 in supine groups ($p = 0.005$). Pronation duration was similar between both RCTs averaging 17 hours each day compared to 20 hours, respectively (Gattinoni et al., 2001; Mancebo et al., 2006). Fernandez et al. (2008) found a positive effect with a long duration of pronation at 20 hours with an improvement of P/F ratios on day three with a mean (±SD) 234 ± 85 compared to 159 ± 78 ($p = 0.009$) in prone and supine groups, respectively. Guerin et al. (2013) in a landmark RCT found a significant oxygenation benefit with pronation on day three and day five at 172 mm Hg ($p < 0.05$) and 179 mm Hg ($p < 0.01$) mm Hg, respectively. Mechanical ventilation days and ICU LOS had a negative effect with prone compared to supine groups in the Prone-Supine II Study (PSII) while the Proseva trial had slightly less mean (±SD) in ICU LOS with prone survival groups 24 ± 22 days in prone compared to 26 ± 27 days in supine ($p < 0.87$) (Taccone et al., 2009; Guerin et al., 2013). Guerin et al. (2004) reported a mean (STD) ICU LOS at 26.6 (29.6) days in prone groups versus 24.5 (21.9) days in supine groups, and with a MV mean duration of 13.7 (7.8) days versus 14.1 (8.6) with a shorter interval of pronation at eight hours. The Proseva trial was the only RCT that reported successful and statistically significant extubation rates at 78.5% compared to 63.3% in supine groups ($p < 0.001$). Mancebo et al. (2006) found slightly greater ICU LOS in prone groups at 20.5 ± 18.2 days compared to 19.1 ± 23.1 days in supine groups ($p = 0.70$). In six non-COVID-19 ARDS RCTs, statistically significant P/F ratios were noted with the prone intervention from days two through five, and throughout a ten-day pronation RCT. However, ICU LOS was not statistically significant to suggest an improvement with prone positioning between prone and supine groups. Intubation days were not accounted in the reviewed RCTs of pronation as the secondary variables of interest were mechanical ventilation days that were not statistically significant to suggest a positive impact with pronation.

The non-COVID-19 ARDS literature is limited to non-RCTs and not all reports specifically measured the impact of pronation with P/F ratios, ICU LOS, and intubation days. Data in context of the current available literature serves as a reference for comparison. At a regional tertiary center in France, 67 patients (57.3%) with severe ARDS COVID-19 were pronated with a 48% discharge rate, 15% mortality rate, and there was a median ICU LOS of 16 days (Doussot et al., 2020). In Wuhan, China, there was a positive effect with pronation in a six-day retrospective observation study of seven patients as oxygenation increased by 62 from 120 ± 61 mm Hg in supine to 182 ±140 mm Hg in prone ($p = 0.065$) (Pan et al., 2020). In NYC, a cohort study of COVID-19 ARDS patients (n=62) found increases in P/F ratios on days four through seven by 57 mm Hg (15.1%) ($p < 0.001$) (Shelhamer et al., 2021). In a cohort study of COVID-19 ARDS patients in Italy, ICU LOS was 17 days overall (n=89) with 43 who were pronated for a median of 18 hours. In France, a prospective cohort study of COVID-19 ARDS patients (n=67) requiring pronation reported a mean ICU LOS of 16 days (Doussot et al., 2020). There was a potential benefit in P/F ratios between days four through seven based on a cohort study (Shelhamer et al., 2021). The median ICU LOS in two non-RCT COVID-19 studies were reported at 16 days (IQR, 10-22), and 18.1 days (IQR 13.1-26.9) with pronation interventions, respectively (Doussot et al., 2020; Shelhamer et al., 2021).

Synthesis of the Literature

With the exception of two RCTs in this review, the literature of non-COVID-19 ARDS found statistically significant effects of pronation on oxygenation (P/F ratios) validating optimization of lung ventilation through dorsal regions and decreasing intrapulmonary shunting (Gattinoni et al., 2001; Guerin et al., 2004; Fernandez et al., 2008; Guerin et al., 2013). The Proseva trial found statistically significant P/F ratios in prone groups on day three ($p < 0.05$), and day five ($p < 0.01$) (Guerin et al., 2013). One RCT in this review did not show a positive effect in oxygenation with prone methods as P/F ratios were greater in supine groups ($p < 0.06$) (Mancebo et al., 2006). Another RCT was terminated early due to being underpowered with limited enrollment (Fernandez et al., 2008). In the same study, Fernandez et al. (2008) found mechanical ventilation (MV) duration with a mean (±SD)11.9 (9.2) days in prone groups compared to Guerin et al. (2004) who found MV duration 13.7 (7.8) days in prone positioning. ICU LOS was reported at a mean (±SD) 26.6 (29.6) days in prone position groups by Guerin et al. (2004). In 2013, the Proseva trial evaluated early pronation with increased pronation duration up to 16 hours. There was no statistical significance in prone survivor groups with a mean (±SD) ICU LOS of 24 ± 22 days compared to 26 ± 27 in supine groups (p = .053). Non-survivor prone groups reported a mean ICU LOS of 21 ± 20 days compared to non-survivor supine groups at 18 ± 15 (p = .053) (Guerin et al., 2013).

Not all patients will improve with pronation as this is a potential strategy for refractory hypoxemia (Hadaya & Benharash, 2020; Berlin et al., 2020). The benefits are improved aeration of lung parenchyma improving oxygenation and has translated into decreasing mortality rates based on a non-COVID-19 ARDS RCT (Guerin et al., 2013).

Use of ARDS Definition

The Proseva trial was published in 2013 and utilized the previous AECC criteria of ARDS defined as acute hypoxemic respiratory failure with a P/F ratio ≤ 200 mmHg with chest radiograph evidence of bilateral infiltrates, and no left atrial hypertension (Ranieri et al., 2012). Due to the sensitivity of P/F ratios with ventilatory settings, challenges of accurately defining hydrostatic edema, and overall lack of further specificities for the complexities of ARDS, the definition of ARDS was updated by an expert panel of international committees (ESICM/ATS/SCCM) (Ranieri et al., 2012). This committee redefined the criteria of ARDS to what is now known as the Berlin Definition of ARDS which was published in 2012. The Berlin Definition improved predictive validity and included subgroups of ARDS (i.e. mild, moderate, severe) categorized by P/F ratio severity, timing in one week of clinical injury or new or further respiratory decompensation, PEEP in all subgroups with at least ≥ 5 cm of water, bilateral opacities not explained by hydrostatic edema or effusions (Ranieri et al., 2012).

Intubation days / ICU

Five RCTs reported LOS as non-primary outcome variables with none showing statistical significance (Guerin et al., 2004; Mancebo et al., 2006; Fernandez et al., 2008; Taccone et al., 2009; & Guerin et al. 2013). The focus of prone positioning randomized trials in ARDS from 2006 to 2009 was driven primarily by understanding the mortality benefit with pronation.

Doussot et al. (2020) found in a COVID-19 ARDS cohort study of prone positioning that the median ICU LOS was 16 days, 48% were discharged home, and the mortality rate was 15% with 30% remaining in the ICU at the time of the study. ICU LOS did not have a statistical significance in five RCTs as two non-RCTs did not report ICU LOS, and one study did not report statistical power of LOS. Ventilation duration was reported in three studies and not statistically significant (Fernandez et al., 2008; Taccone et al., 2009; Guerin et al., 2013). The Proseva trial was the only RCT with a statistically significant mortality outcome in addition to successful extubation rates and ICU discharges (Guerin et al., 2013). Pan et al. (2020) was the only COVID-19 observation study from Wuhan, China included in this manuscript that found a statistically significant improvement in lung recruitment ($p = 0.020$) with pronation compared to supine measurements. Oxygenation index improved in pronation with a P/F ratio of 120 ± 61 mm Hg supine to 182 ± 140 mm Hg in prone positioning. However, these results were not statistically significant ($p = 0.065$) (Pan et al., 2020). In Italy, 170 non-COVID-19 ARDS patients undergone pronation and found improved oxygenation as a result with a mean duration of pronation at nine hours ($p < 0.0001$) (Lucchini et al., 2020). LOS was 20 days with a 58% ICU discharge and survival rate (Lucchini et al., 2020).

Duration of Prone Positioning and Technique Used

Five studies instituted longer duration of prone positioning from 16 to 20 hours per day. Gattinoni et al. (2001) and Guerin et al. (2004) were the only randomized trials with minimal prone positioning duration from seven to eight hours per day. There were logistical and staffing issues with pronation noncompliance in 41 patients that may have limited the overall effectiveness of the study results and pronation process (Guerin et al., 2004). P/F ratios increased by 63 mm Hg versus 44.6 mm Hg in the prone and supine cohort, respectively ($p < 0.02$) (Gattinoni et al., 2001). Also significant were new or worsening pressure ulcers in prone groups ($p = 0.004$) (Gattinoni et al., 2001). Guerin et al. (2013) and Lucchini et al. (2020) were the only studies that provided specific procedural technique of how nursing staff were to manually implement pronation with standard ICU beds. The PS II study was the only RCT that included a mixture of Rotoprone and standard ICU beds. Rotoprone beds were utilized greater in 20 centers compared to five centers with manual pronation methods. There was no survival benefit based on technique, nor significant outcomes in ventilation days and ICU LOS (Taccone et al., 2009).

Ethical Considerations

The COVID-19 pandemic has brought on ethical challenges due to limited resources like mechanical ventilators, and ICU beds causing rationing care decisions of who and what criteria is needed to guide the clinicians' decisions of who is provided life saving measures. In Northern Italy, caregivers had moral distress due to observing death directly related to a lack of ventilators and the decision making that was undisclosed due to the shear difficulty of sharing the experiences. Italian physicians in the Lombardy region took into consideration age, comorbidities, severity of respiratory failure, and the utilitarian principle of saving the most with the best chances to survive (Rosenbaum, 2020). Physicians had to lower the age range from 80 to

75 at one hospital due to ventilator scarcity and the slow weaning process of ventilators and increasing duration up to 15 to 20 days. A prolonged ventilatory course for an elder patient may deny the opportunity for a younger patient to have a ventilator. The moral distress of rationing care prompted ethical counsel by the Italian College of Anesthesia, Analgesia, Resuscitation, and Intensive Care (SIAARTI) and recommended clinical reason and utilitarian approaches to help guide rationed care (Rosenbaum, 2020). Another example of ethical decision making highlighted a clinical framework that was led by an intensivist and community members in Maryland. They collaborated to guide ethical decisions with ventilator allocation during disasters and found three principles to guide ethical practice. First, was to include a triage officer with nursing and respiratory experts to communicate with the care team, patient, and family. Second, to have a regulatory state level monitoring committee, and lastly a triage algorithm that is adapted to change with current research investigations (Rosenbaum, 2020).

The City and County of Los Angeles at the height of the COVID-19 surge prepared for resource allocation during crisis level of care. Hospitals notified the California Department of Public Health that were functioning at crisis care levels. The secretary of California's Health and Human Services conveyed that hospitals were making difficult decisions and were exhausted (Lin et al., 2021). Triage officers were appointed to facilitate the supply and demands of hospital resources (i.e. ICU nurses, ventilators, ICU beds, oxygen) with administrators, emergency room leadership, and ICUs to assess the daily situation during the surge (Los Angeles Department of Health Services [LADHS] 2020). Decisions were to be made with communication of nursing directors, physicians, patients, and families. Patient families had the right for reconsideration of decisions and to obtain a second medical opinion. The goal for public health ethics during crisis level of care is to do the most good for the most people. In terms of moral obligation for front line workers, health care workers have a duty to the patient to provide the best care with the available resources (LADHS, 2020).

The ethical considerations of this project complied with data privacy and confidentiality laws. There were no direct interventions tested on subjects as this was a retrospective chart review. Patients' data privacy was maintained, and risks were minimized with utilization of encrypted internet connection during the data collection. No patient identifiers were used to compromise data privacy.

Gaps in the Literature

Pronation is a rescue therapy for COVID-19 ARDS patients and pronation clinical outcomes of P/F ratios, ICU LOS, and intubation days have not been evaluated. Shelhamer et al. (2021) found in a cohort study in South Bronx, New York City that pronation improved oxygenation from days four through seven, and reduced mortality rates in COVID-19 ARDS. ICU LOS was reported at a median of 18.1 days. COVID-19 prone positioning studies are being published to describe the process, protocols, and mortality outcomes (Binda et al., 2021; Doussot et al. 2020). However, pronation outcomes about oxygenation, ICU LOS, and intubation days during the COVID-19 pandemic are lacking. Evidence supports ongoing pronation interventions. However, until what extent is pronation ineffective is not reported with respect to the clinical course of ARDS. In addition, one study reported nursing staff to have back pain, joint pain, and anxiety related to pronation processes (Doussot et al., 2020). The scientific inquiry of testing what the outcomes are with pronation and if they are beneficial needs exploration to substantiate the moral duty of providing an intervention that is otherwise rescue treatment. The risks can be both traumatic to clinicians and patients who undergo this resource and physical intensive endeavor particularly in a pandemic surge like COVID-19.

Chapter Four: Methods

Project Design

This project used a retrospective data analysis and comparative design of COVID-19 ARDS adult patients compared with non-COVID ARDS age and gender matched historical control group. Institutional Review Board (IRB) has been exempted by UCLA General IRB. An IRB exemption was approved by UCLA Health based on the previous decision held by UCLA General IRB that stated this project does not meet the definition of human subject research and therefore exempt from IRB.

Sample and Setting

The setting was at a single center quaternary academic hospital MICU in Los Angeles, California, United States. A convenient sample of intubated COVID-19 patients with moderate to severe ARDS met inclusion criteria in the prospective arm of the study. The historical control group was age and gender matched controls of non-COVID ARDS patients from a retrospective chart review of five years prior to February 2020. The comparison group was obtained through a convenient sample from the same quaternary academic center MICU department matching gender and age ± three years. The retrospective data search was facilitated through a health informatics department in a quaternary medical center in Los Angeles during the COVID-19 pandemic. A formal patient data request of a MICU was made through requesting an International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10) code of COVID-19 (U07.1) from March 2020 to April 2021. A second request for the ICD code of ARDS (J80) was made for a five-year retrospective data search between January 2015 to December 2019.

Inclusion criteria for all ARDS cases was adult patients ≥ 18 years of age who met the Berlin Definition of acute-onset (within one week of known clinical insult or new / worsening respiratory symptoms), moderate and severe ARDS 1) Moderate ARDS is P/F ratio of 100 to 200 mm Hg and a PEEP ≥ 5 cm of water. 2) Severe ARDS is a P/F ratio ≤ 100 mm Hg and PEEP ≥ 5 cm of water, or 3) new or decompensating respiratory clinical status that is confirmed on imaging with bilateral opacification of the lungs not explained by effusions, lobar/lung collapse, or nodules, and where respiratory failure is not completely explained by pulmonary permeability from cardiac failure or fluid volume overload by clinical determination of a physician. If there are no ARDS risk factors, an objective assessment like echocardiography is required to exclude hydrostatic edema (Ranieri et al., 2012).

COVID-19 median time of onset of symptoms to ARDS diagnosis is eight to 12 days, and time to ICU admission from onset of COVID-19 symptoms is 10 to 12 days (CDC, 2020). This is an atypical variability of ARDS diagnosis in COVID-19 as compared to non-COVID-19 ARDS which met identification within seven days of a known clinical symptom. However, the Berlin criteria also included new or decompensating respiratory symptoms as an alternative to meet inclusion criteria. Exclusion criteria included cases of ARDS patients who were not intubated and not pronated at least once for the duration of the 16-hour protocol. A total of 90 charts of COVID-19 patients were obtained, of which, 41 made inclusion criteria and 49 were excluded due to non-ARDS cases, private files, non-intubated cases on high flow nasal cannula, do not intubate directives, and inability to tolerate proning to sufficiently gather at least one day of pronation intervention. The non-COVID-19 ARDS group yielded 56 charts through the informatics ticket request of charts for ICU-code J80 from January 2015 to December 2019. Six cases met inclusion criteria for this project as 50 were excluded due to non-ARDS diagnosis per

Berlin Definition, non-intubated status, do not intubate directive, and less utilization of prone positioning and less available data to measure. Appendix 1 shows the inclusion and exclusion criteria for COVID-19 ARDS and non-COVID-19 ARDS groups in this study.

For COVID-19 ARDS cases, the Berlin Definition of moderate and severe ARDS was applied along with a positive nucleic acid amplification testing (NAAT) also known as a reverse-transcription polymerase chain reaction (RT-PCR) assay nasopharyngeal or oropharyngeal swab specimen as this is the diagnostic method of choice for COVID-19 (CDC, 2020). Radiographic diagnostic criteria included chest radiograph and chest computed tomography that has limited evidence to diagnose COVID-19 alone and is not recommended by the CDC and American College of Radiology (ACR) as radiographic evidence suggestive of COVID-19 requires viral testing to confirm a positive diagnosis despite clinically favorable radiographic findings of COVID-19 (CDC, 2020; ACR, 2020).

Sample Size

A convenience sample was collected according to diagnostic criteria of COVID-19 and ARDS who was provided at least one prone positioning intervention with a baseline before pronation P/F ratio of $\leq$ 150 mm Hg. G* power 3.1 software was utilized to provide an *a priori* power analysis and indicated that a sample size of 128 subjects (64 being historical controls) would allow a detection of a moderate (d=0.5) effect size on a two-tailed independent t-test with alpha of 0.05 and power=.80.

Pronation Protocol Guidelines

Pronation was instituted for patients diagnosed with ARDS when P/F ratios were less than 150 mm Hg with a FiO_2 of 60% or greater and a PEEP of 5 cm of water. COVID-19 ARDS patients were pronated for 16 hours and turned 8 hours in supine position until P/F ratios were greater than 150 mm Hg. Skin protective precautions were utilized using Mepilex on high-risk pressure areas like the chest, face, forehead, knees, and hips. Fluidized pillows also were utilized to protect ears and cloth tape to help prevent pressure injuries around the mouth with endotracheal tubes. Pronation was stopped when P/F ratios were greater than 150 mm Hg or if pronation was not tolerated due to unstable hemodynamics or further respiratory decompensation such as oxygen de-saturation.

Data Collection

Retrospective data was obtained through utilizing the institution's electronic medical record (EMR). The characteristics of age, gender, BMI, P/F ratios, ICU LOS, intubation days, successful extubation, tracheostomies, amount of time until first pronation intervention, pressure ulcers, and survival were recorded on a prone positioning excel spreadsheet between the two cohorts. P/F ratios were gathered by an arterial blood gas (ABG) that was recorded on the EMR. The P/F ratios were collected before pronation, and at the end of pronation for each intervention day up to 28 days. Data about the intervention were not collected after pronation was discontinued, or if the pronation sequence was stopped due to patients not tolerating pronation, expiring, or due to transitioning to comfort care. Only seven days of P/F ratios were measured and analyzed in this study due to the attrition rate as the total sample size in the COVID-19 ARDS group decreased by 68.3% by day seven, and the non-COVID-19 ARDS group diminished by 66.7%.

Primary and Secondary Outcomes

The primary dependent variables are P/F ratios, ICU LOS, and intubation days. Secondary outcomes are modeled after the Proseva trial and will analyze successful rates of extubation, tracheostomy rates, and survival rates. Mechanical ventilation duration reports in

Italy during the first COVID-19 surge ranged from six to 17 days and the LOS ranged from six to 21 days (Grasseli et al., 2020). P/F ratios in this study were measured up to 28 days of intubation and pronation. Successful extubation is defined as no reintubation or utilization of noninvasive ventilation in 48 hours post extubation (Guerin et al., 2013). This was followed by a medical review of age ± three years, and gender matched ARDS patients who were in the same hospital unit pre-COVID-19.

Statistical Analyses

Primary outcomes of P/F ratios, intubation days, and ICU LOS are numeric and were compared between COVID-19 ARDS and non-COVID-19 ARDS groups using nonparametric testing of Mann-Whitney U. The Wilcoxon Signed Rank Test analyzed the daily oxygenation benefit of pronation before and at the end of the intervention. Cohen's d was utilized to examine effect size for non-statistically significant comparisons. Variables were expressed as mean (STD), median, and interquartile range (IQR). Group differences based on demographic and clinical variables were described using descriptive statistics (mean, SD, percentages). Data analysis was done using SPSS version 26.0. The hypothesis is pronation improves P/F ratios, shortens intubation days, decreases ICU LOS and produces similar results between COVID-19 and non-COVID-19.

Chapter Five: Results

COVID-19 ARDS Compared to non-COVID-19 ARDS

During April 2020 to February 2021, there were 90 patient charts retrieved with the diagnosis of COVID-19 in the MICU. Of these charts, 41 COVID-19 ARDS met inclusion criteria for this project. The comparison group of non-COVID-19 ARDS yielded 56 total patients. Of these 56 non-COVID-19 patients, there were six patients who met inclusion criteria for this project and 50 who were excluded due to a lack of prone interventions, accurate documentation, and inconsistent ABG measurements to sufficiently measure before pronation and end of pronation positioning. Table 1 shows the demographic and clinical characteristics of the 47 patients included in the study analyses.

Table 1: *Characteristics*

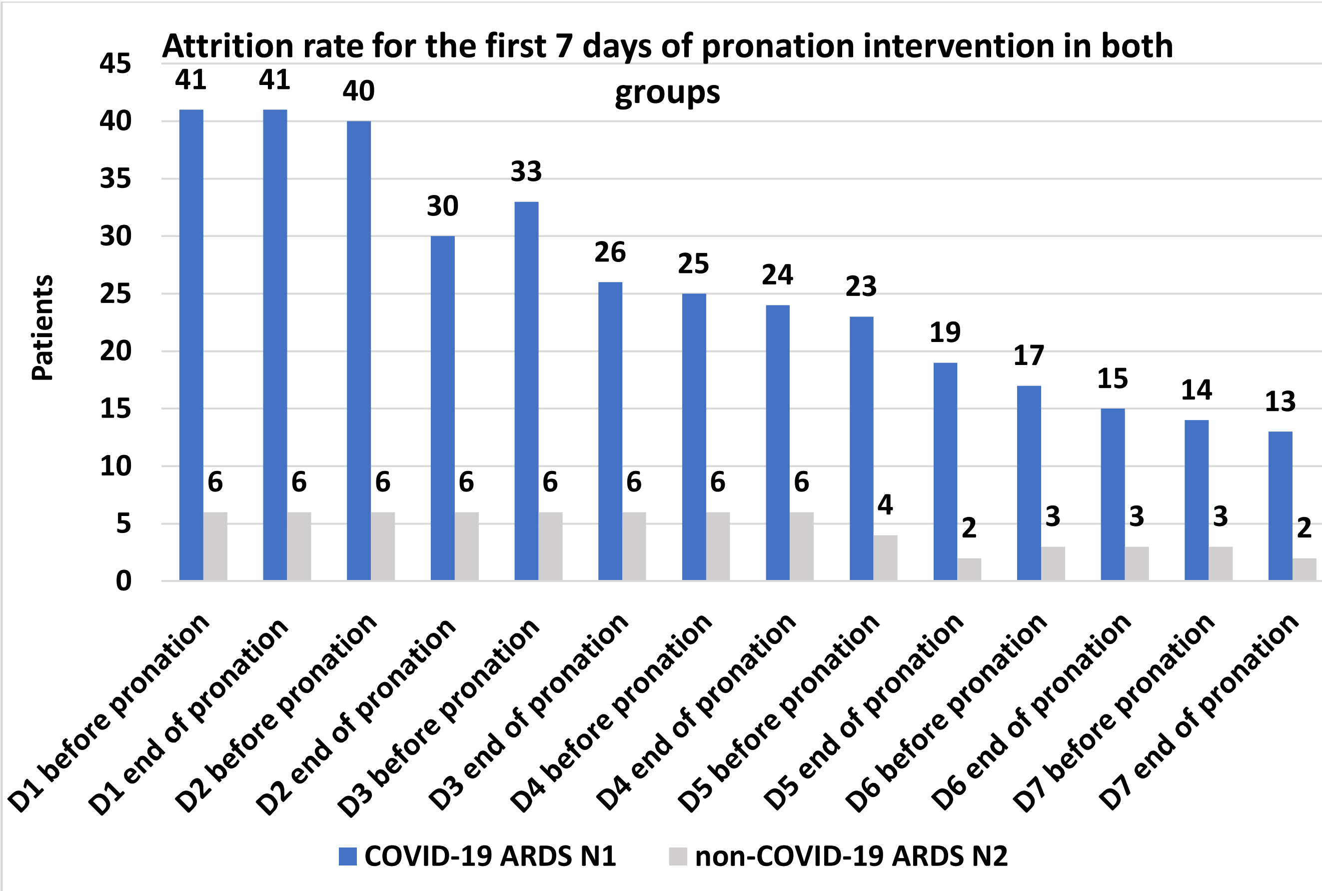
Characteristics	**COVID-19 ARDS**	**non-COVID-19 ARDS**
Age (standard deviation [STD])		
	62.1 (STD=13.3)	50.7 (STD=8.96)
Gender No. (%)		
Female	16 (39%)	3 (50%)
Male	25 (61%)	3 (50%)
BMI		
	30.6 (STD=11.7)	27.7 (STD=5.66)
ARDS etiology No. (%)		
Influenza	0	1 (16.7%)
Rhinovirus	0	1 (16.7%)
Septic shock	0	2 (33.3%)
CMV pneumonia	0	1 (16.7%)
Idiopathic pneumonia	0	1 (16.7%)
COVID-19 viral pneumonia	41 (100%)	0
Race No. (%)		
African American	2 (4.9%)	1 (16.7%)
Asian / Pacific Islander	3 (7.3%)	0
Hispanic	23 (56.1%)	2 (33.3%)
White	7 (17.1%)	3 (50%)
Middle Eastern	1 (2.4%)	0
Other	3 (7.3%)	0
Comorbidities No. (%)		
Cancer	9 (22%)	3 (50%)
Cardiac disease	2 (4.8%)	0
Alcoholic cirrhosis	0	1 (16.7%)
NASH	3 (7.3%)	0
Hepatitis C	2 (4.9%)	0

CKD	2 (4.9%)	0
Diabetes	14 (34.1%)	0
ESRD	3 (7.3%)	1 (16.7%)
HIV	1 (2.4%)	0
HTN	19 (46.3%)	0
Hyperlipidemia	7 (17.1%)	0
Organ transplant No. (%)		
Stem cell transplant	1 (2.4%)	3 (50%)
Kidney transplant	3 (7.3%)	0
Liver transplant	4 (9.8%)	0
Lung transplant	3 (7.3%)	0
Neurologic No. (%)		
TIA	1 (2.4%)	0
Ischemic stroke	1 (2.4%)	0
Aneurysm s/p clipping	1 (2.4%)	0
Brain tumor	1 (2.4%)	0
Pulmonary disease No. (%)		
COPD	1 (2.4%)	0
Pulmonary fibrosis	1 (2.4%)	0
Hypersensitivity pneumonitis	1 (2.4%)	0
Obstructive sleep apnea	2 (4.9%)	0
Pulmonary embolism	2 (4.9%)	0
Metastatic lung cancer	1 (2.4%)	0
Smoker No. (%)		
Former	9 (22%)	0
Unknown	6 (14.6%)	2 (33.3%)
No	26 (63.4%)	4 (66.7%)

Ages averaged 62.1 years (standardized deviation [STD]=13.3) in COVID-19 ARDS group compared to 50.7 YEARS (STD=8.96) in non-COVID-19 ARDS. The COVID-19 ARDS group was 61% male and 39% female. Non-COVID-19 gender was even at 50%. Body mass index (BMI) reported at 30.6 kg/m^2 (STD=11.7) compared to 27.7 kg/m^2 (STD=5.66) in non-COVID-19 ARDS. Causes of ARDS in COVID-19 patients were related to direct lung injuries (pulmonary) from viral pneumonia compared to non-COVID-19 ARDS patients that were also related to direct lung injury etiologies of pneumonia secondary to influenza, rhinovirus, cytomegalovirus (CMV) pneumonia, and idiopathic pneumonia. Two cases of ARDS were secondary to an indirect lung injury (extrapulmonary) related to septic shock. The study sample was 56.1% Hispanic in the COVID-19 ARDS group compared to 33.3% in non-COVID-19 ARDS group, while White patient population was reported at 17.1% compared to 50%, respectively. The African American and Asian / Pacific Islander patient population was 4.9% and 7.3% in COVID-19 ARDS while in non-COVID-19 ARDS, African American and Asian / Pacific Islander made up 16.7% and 0%, respectively. The most common comorbidities were hypertension, diabetes, and cancer in COVID-19 ARDS while stem cell transplant and cancer were the most common comorbidities in non-COVID-19 ARDS. All patients were intubated or transferred from an outside hospital intubated and mechanically ventilated.

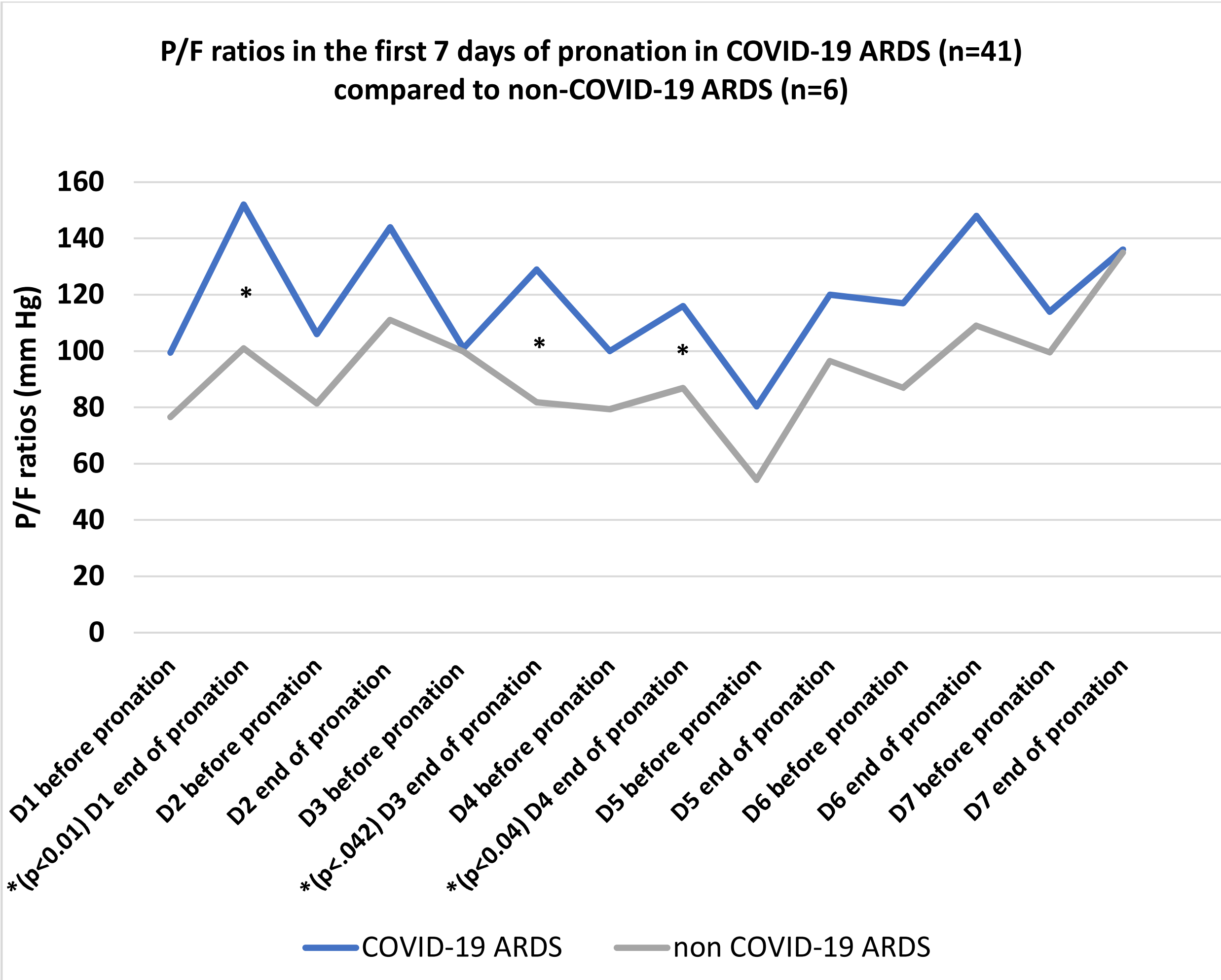
There was a substantial attrition rate due to non-survival, transition to comfort end of life care that limited our data collection of the pronation intervention to seven days. By intervention day seven, the COVID-19 ARDS group dropped by 68.3% compared to a 66.7% drop in the non-COVID-19 ARDS group at day seven. Thus, our retrospective data collection of P/F ratios before pronation *vs* end of pronation was limited to seven days of pronation interventions.

Figure 1: *Attrition rate*



Prone Positioning and P/F ratios in COVID-19 ARDS (n=41) vs non-COVID-19 ARDS Groups (n=6)

Figure 1: *P/F ratios of COVID-19 ARDS (n=41) vs non-COVID-19 ARDS (n=6)*



For day one of P/F ratios at the end of pronation in the COVID-19 ARDS group, there were statistically significant results with a large effect size. The P/F ratios at the end of pronation for the COVID-19 ARDS group (mean = 152, standard deviation [std] = 60.8; median = 143, interquartile range [IQR] = 55) compared to the non-COVID-19 ARDS group (mean = 101, STD = 45.9; median = 89.3, IQR = 81.1). The difference between groups was statistically significant (Mann-Whitney U = 42, p = 0.01). We also examined the difference between before pronation and end of pronation P/F ratios in the COVID-19 ARDS group to determine the impact of pronation on P/F ratios before pronation compared to end of pronation, a Wilcoxon Signed Rank Test found statistically significantly positive effects with P/F ratios end of pronation compared to

P/F ratios before pronation ($p < 0.001$). In the non-COVID-19 ARDS groups, P/F ratios at the end of pronation were greater than before pronation, but the difference was not statistically significant ($p = 0.463$). The duration of pronation (hours) in day one was greater at 16.9 hours (STD = 4.34) in COVID-19 ARDS compared to the non-COVID-19 ARDS group at 15.8 hours (STD = 3.93). The difference was not statistically significant between the groups ($p = .543$).

On day three of prone positioning, P/F ratios at the end of pronation were statistically significantly greater in the COVID-19 ARDS group (mean = 129, STD = 70.8; median 142, IQR = 77.5) compared to the non-COVID-19 ARDS group (mean = 81.8, STD = 57.6; median 97.5, IQR = 105). The difference between the groups were statistically significant (Mann-Whitney U = 36, $p = 0.042$). To determine the impact of pronation on P/F ratios before pronation compared to the end of pronation, a Wilcoxon Signed Rank Test showed a statistically significant positive effect in P/F ratios before pronation ($p = 0.015$) in the COVID-19 ARDS groups compared to the non-COVID-19 ARDS group ($p = .273$). The mean pronation duration on day three was 16 hours (STD = 5.07) in the COVID-19 ARDS group compared to the non-COVID-19 ARDS group at 12.7 hours (STD = 10.1). The difference was not statistically significant between the groups ($p = 0.904$).

Statistically significant P/F ratios end of pronation results were also found on day four, in the COVID-19 ARDS group (mean = 116, STD = 60.9; median = 133, IQR = 81.5) compared to non-COVID-19 ARDS group (mean = 86.8, STD = 63.3; median = 99 IQR = 118). The difference between the groups was statistically significant (Mann-Whitney U = 32.5, $p = 0.04$). To further determine the impact of pronation on P/F ratios before pronation *vs* end of pronation, a Wilcoxon Signed Rank Test showed statistically significant positive trends in P/F ratios before pronation on day four ($p = 0.011$) in the COVID-19 ARDS group as compared to the non-

COVID-19 ARDS group where P/F ratios before pronation had a non-statistical significance with end of pronation P/F ratios only slightly greater than before pronation (p = .593).

Figure 2: *The Wilcoxon Signed Rank Test and impact of pronation with daily P/F ratios in COVID-19 ARDS*

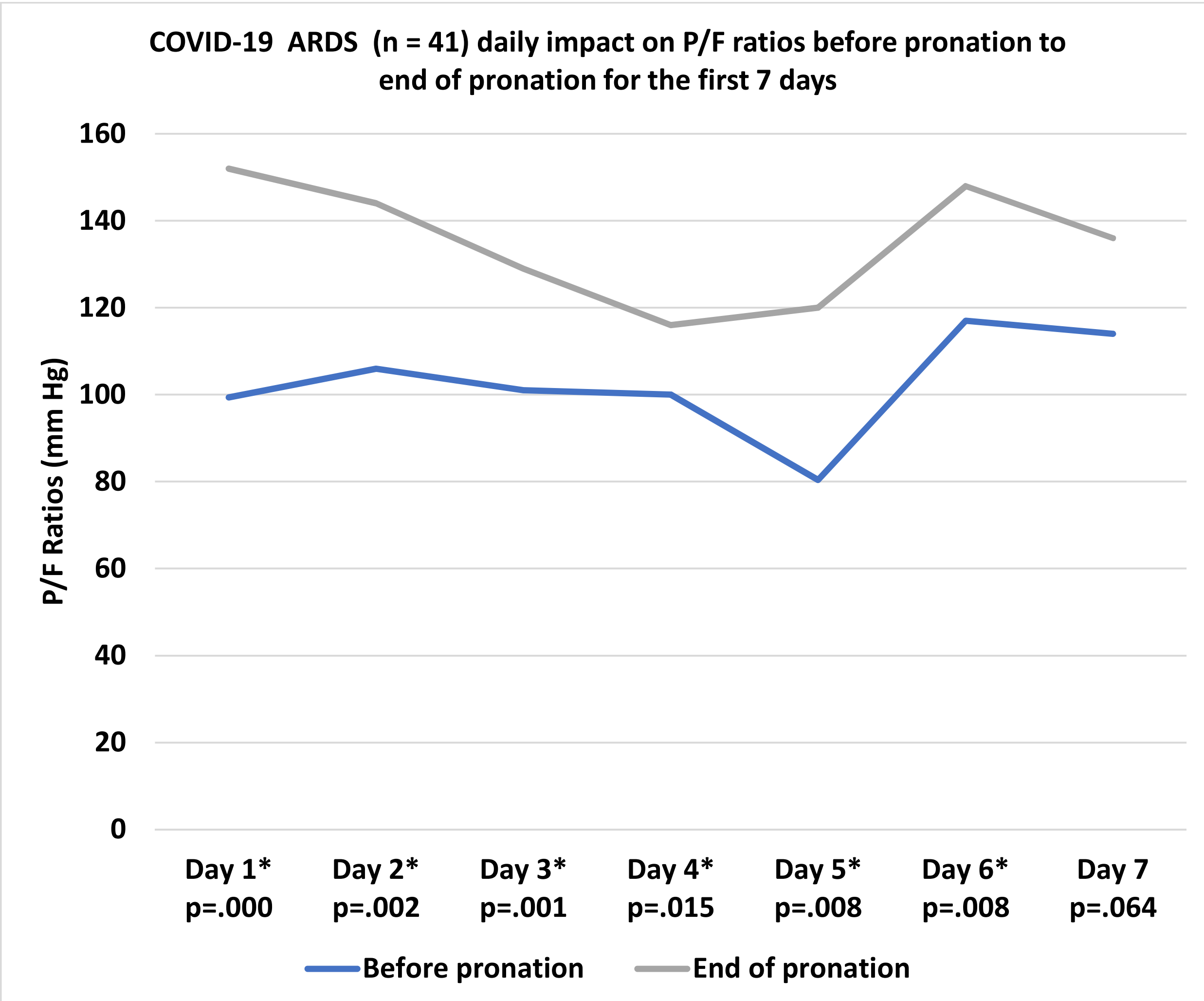
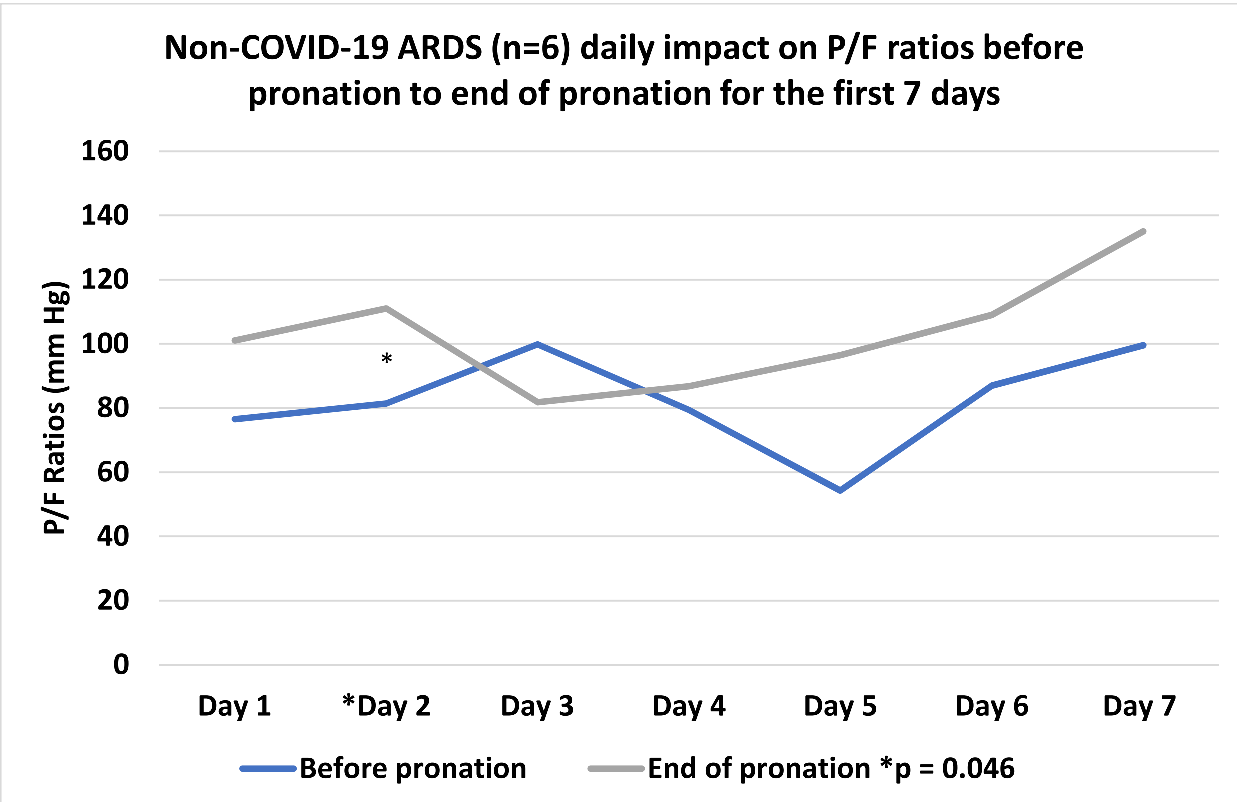


Figure 3: *The Wilcoxon Signed Rank Test and impact of pronation with daily P/F ratios in non-COVID-19 ARDS*



The Wilcoxon Signed Rank Test found statistically significant results with P/F ratios between before pronation and end of pronation differences in days one through six in the COVID-19 ARDS group ($p < 0.05$). However, in the non-COVID-19 ARDS group, only day two provided statistical significance in P/F ratios between before pronation and end of pronation cycles ($p < 0.046$). The difference between groups may be related to the stages of ARDS in respective groups. In addition, the COVID-19 ARDS group had aggressive pronation procedure and thus early pronation interventions at a mean of 33.2 hours (STD = 42.9) compared to the non-COVID-19 ARDS group starting pronation interventions comparatively later at 116 hours

(STD = 172) or 3.45 days later than the COVID-19 ARDS group. However, the difference was not statistically different between the groups (p = .244).

Prone Positioning and ICU LOS

The mean ICU LOS in the COVID-19 ARDS group was 24 days (STD = 17.6; median = 18, IQR = 19.5) as compared to the non-COVID-19 ARDS group at 21.5 days (STD = 17; median = 14.5, IQR = 24.4). The difference between groups was not statistically significant (Mann-Whitney U = 106, p = .587). In the survival subgroup of the COVID-19 ARDS group (n = 12), ICU LOS was 33.8 days (STD=15.7; median = 38, IQR = 23.8) compared to non-survival groups (n = 29) at 19.9 days (STD=19.9; median = 15, IQR = 11.5). There were no survivors in the non-COVID-19 ARDS group (n = 6).

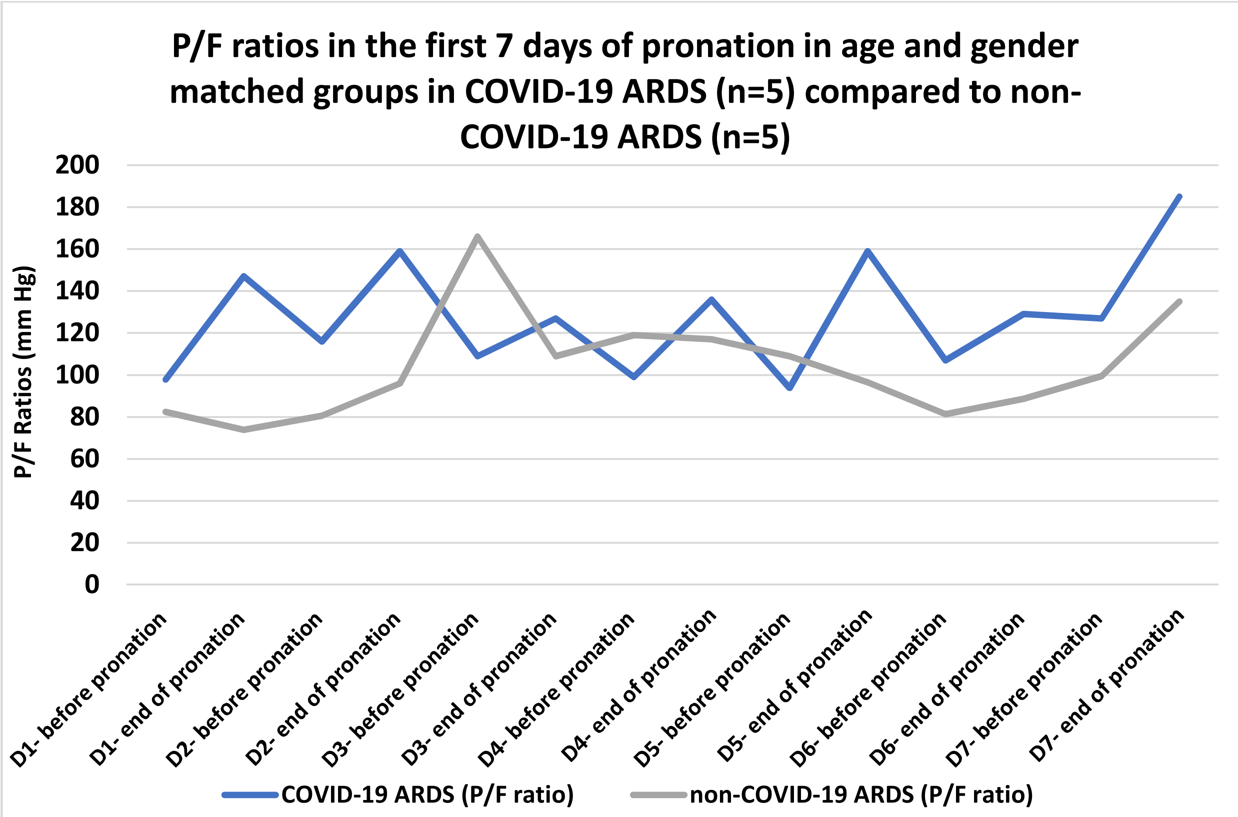
Prone Positioning and Intubation days

Intubation days were collected by time of intubation to extubation or tracheostomy insertion for both COVID-19 ARDS and non-COVID-19 ARDS groups. The mean intubation days in the COVID-19 ARDS group was 16.2 days (STD = 11.7; median = 14, IQR = 11) compared to the non-COVID-19 ARDS group at 14.9 days (STD = 7.37; median = 11, IQR 12.7). The difference between groups were not statistically different (Mann-Whitney U = 114, p = .762). The mean intubation days of those that survived COVID-19 ARDS was 18.4 days (STD = 11.6; median = 16.5, IQR = 14.8). There were no survivors in the comparison group.
The non-survivors in the COVID-19 ARDS group had a mean 15.2 days (STD = 11.7; median = 13.0, IQR = 10.5) compared to intubation days of the non-COVID-19 ARDS group with a mean of 14.9 days (STD = 7.37; median = 11.0, IQR = 12.7).

Age and Gender Matched Groups

***Pronation and* P/F ratios**

Figure 4: *P/F ratios in age and gender matched groups*



While we did not find statistically significant results for P/F ratios in seven days of prone positioning with age and gender matched groups analyzed, it is important to note that Cohen's d effect size was large for outcomes of P/F ratios on day one end of pronation (d = 1.14), day two before pronation (d = .875), day five end of pronation (d = 2.44), day six before pronation (d = .995), day six end of pronation (d = .995), and day seven before pronation (d = .995). At the end of pronation on day seven, there was a moderate effect size (d = .564).

Age and Gender Matched Groups: Prone Positioning and ICU LOS

The mean ICU LOS in the COVID-19 ARDS group was 19.6 days (STD = 13.3; median = 16.0, IQR = 24.0) compared to the non-COVID-19 ARDS groups at 23.9 days (STD 17.7; median = 19.0, IQR = 30.4). The difference between the two groups was not statistically significant (Mann-Whitney U = 9, p = 0.46). It is important to note that the Cohen's d effect size was medium (d = 0.475).

Age and Gender Matched Groups: Prone Positioning and Intubation Days

The mean intubation days in the COVID-19 group was 12.2 days, STD = 4.44; median = 11, IQR = 8) as compared to the non-COVID-19 group at 16 days (STD = 7.65; median = 12, IQR = 14). The difference between the two groups was not statistically significant (Mann-Whitney U = 8, p = 0.346). The Cohen's d size found a medium effect size (d = 0.623).

Supplemental Information of Pronation in Both Groups

The mean prone positioning cycle in the COVID-19 ARDS group occurred at an average of 13.6 times (STD = 11.2; median = 8.5, IQR = 8.25). From the time (hour) of intubation, medical optimization, and provider order, prone positioning first occurred within an average of 33.2 hours (STD = 42.9; median = 23.4, IQR = 25.7). The non-COVID-19 ARDS group had pronated with less frequency compared to the COVID-19 ARDS group (mean = 5.12, STD = 2.64; median = 5.00, IQR = 4.75). The time frame of when pronated first started in relationship to intubation and ARDS diagnosis occurred later in the non-COVID-19 ARDS group (mean = 116 hours, STD = 172; median = 41.4, IQR = 197).

Prone Positioning and Pressure Ulcers

Protocolized procedure for pressure ulcer prevention with pronation was instituted with protective polyurethane absorbent foam dressings known as Mepilex. These were applied to pressure areas at high risk of breakdown prior to pronation including the feet, knees, hips, cheeks, chest, and forehead. A fluidized pillow allowed prone teams to tailor pillow with head rotations with relationship to the endotracheal tube and positioning of ears. Additional supportive pillows were utilized under the chest, and on each limb, hips, shins, and toes. With skin protective techniques in place, there were a total of 14 pressure ulcers in 41 charts reviewed for COVID-19 ARDS patients who undergone at least one pronation cycle. Twelve pressure ulcers were likely related to pronation as pressure ulcers were documented in various anatomical ventral sites (i.e. cheek, ear, face, nose, chin, chest, shins, and perineum). One patient was pronated 39 times sustaining a deep tissue injury (DTI) on the umbilicus. Another patient developed a stage II pressure ulcer noted on the cheek. Two pressure ulcers that were reported were not related to pronation as the origin of the ulcer was on the sacrum in the COVID-19 ARDS group. In comparison to the non-COVID-19 ARDS group, there were three pressure ulcers reported in six cases on the dorsal region of the sacrum and gluteal fold less likely related to prone positioning. Skin protection practice at this academic institution had lower rates of pressure injuries compared to a rigorous non-COVID-19 ARDS RCT.

Chapter Six: Discussion

Oxygenation improved in our study comparable to results of non-COVID-19 ARDS randomized trials (Gattinoni et al., 2001; Guerin et al., 2004; Mancebo et al., 2006; Fernandez et al., 2008; Guerin et al., 2013). The DNP project-lead found an oxygenation benefit with pronation in the first week that is also comparable to a retrospective study in NYC during the COVID-19 pandemic that found an increase in P/F ratios on day four through seven ($p < 0.001$) (Shelhamer et al., 2021). Early pronation is consistent with the pronation design standardization in the Proseva trial where intubated patients were randomized within 36 hours of intubation with a 12-to-24-hour stabilization period for randomization and pronated within one hour for 16 hours after the inclusionary period (Guerin et al., 2013).

In this retrospective study, pronation occurred within a mean 33.2 hours (STD = 42.9) of intubation and medical stabilization in COVID-19 ARDS compared to 116 hours (STD=172) in the non-COVID-19 ARDS group. The difference was not statistically significant ($p = 0.244$). However, an oxygenation benefit was found in COVID-19 ARDS compared to non-COVID-19 ARDS with early pronation where an assertive unit-based protocol was established. The DNP project-lead speculates the difference in P/F ratios between groups is related to early pronation in the COVID-19 ARDS group within the early exudative stage in ARDS. Pronation is rescue therapy in COVID-19 ARDS and based on these findings, further investigation is recommended into the effect of assertive pronation protocol practice with particular focus in the first week of intubation.

The DNP project-lead initially hypothesized that ICU LOS and intubation days can be shortened with pronation. However, the data did not show statistical significance, and the sample size was underpowered. ICU LOS and intubation days in non-COVID-19 ARDS were also not statistically significant in a number of other studies (Guerin et al., 2004; Mancebo et al., 2006; Fernandez et al., 2008; Taccone et al., 2009; & Guerin et al., 2013).

It is important to distinguish the purpose of collecting intubation days versus mechanical ventilation days as the focus in this study. The reason to measure intubation days was influenced by the pandemic surge that brought a health care crisis to the City and County of Los Angeles. ICU bed and ventilator availability were of concern and aggressive triaging of patients out of the ICU to open beds and to take oncoming rapid cycles of decompensating severe-COVID-19 patients were taking precedence. It was important to safely transition surviving patients to long term care or subacute ventilator units to safely open ICU bed capacity. These results were not statistically significant to suggest pronation impacted intubation days.

There were 12 patients (29%) who had tracheostomies and three in this subgroup that did not survive. However, three patients were successfully extubated and survived. Successful extubation in this study was defined as no re-intubation after 48 hours of extubation, nor the use of noninvasive ventilation. Intubation days/mechanically ventilated days in this subgroup of three successfully extubated patients were less than the general group at a mean seven days (STD = 1). In the non-COVID-19 ARDS group, there were no successful extubations nor patients who were able to transition to tracheostomies after pronation.

There were 12 patients in the COVID-19 ARDS group who developed pressure injuries related to pronation intervention (29%) as compared to the non-COVID-19 ARDS literature at 14% (n=23) (Lucchini et al., 2020), and one RCT with 44.4% at ICU discharge (n=237) (Girard et al. 2014). One cross-sectional study at a hospital hub in Lombardy, Italy during the COVID-19 pandemic found pressure ulcers at 30.2% related to pronation, and the face was the most affected site (Binda et al., 2021). Most pressure injuries possibly had greater occurrences due to prolonged prone positioning greater than the protocol (>16 hours). The prone positioning protocol and current recommendations are 12 to 16 hours based on evidence-based practice. Often in refractory hypoxemic COVID-19 ARDS cases, de-saturation would occur after a cycle of pronation (16 hours) when positioned in the supine position and urgently prompting clinicians to re-order pronation protocols continuously greater than 24 hours.

Practice considerations can possibly re-evaluate the benefits versus risks involved with prolonged pronation practice (> 16 hours) and to consider the stage of ARDS with clinical presentation before ongoing pronation interventions. The nursing protocol as to when to stop pronation is based on clinician judgement and if P/F ratios are greater than 150 mm Hg. The incorporation of the stages of ARDS to pronation protocols (i.e. early exudative, fibroproliferative, fibrotic) can be assessed by intubation days and clinical assessment. Delineation of protocol to the pathophysiological progression of ARDS can improve the overall process of pronation as continuous pronation interventions for over seven to ten days may or may not be beneficial. It is possible that pronation in the fibrotic stage of ARDS is medically ineffective. Further investigation is recommended to evaluate the stage of ARDS with lung mechanics, arterial blood gas analysis, and CT pulmonary imaging. It is hypothesized that pronation would be ineffective in the latter stages of ARDS due to lung fibrosis and further goals of care discussion would be recommended to avoid possible harm with prolonged prone positioning interventions.

Limitations

The sample size was underpowered and did not reach statistical power limiting the generalizability of this study. Cautious interpretation of these results is warranted due to being a single center retrospective comparative study. Clinical decisions are influenced through case-by-case clinical presentation. Further limitation factors were obtaining P/F ratios before pronation and at the end of pronation for daily pronation interventions were not always carried out. The data collection was dependent on accurate nursing, physician, and respiratory technician notation on each pronation and supination intervention. In addition, not all patients with COVID-19 in the ICU had ARDS or were intubated further limiting the sample and effect size. There were rapid rates of respiratory and hemodynamic instability and subsequent high mortality rates precluding pronation intervention all together.

Conclusion

This retrospective study found pronation intervention to be effective in improving oxygenation comparable to pre-COVID-19 RCTs and current available data on COVID-19 ARDS. Pronation did not impact ICU LOS and intubation days. The DNP project-lead speculates the improvement in oxygenation is related to an early pronation protocol that was instituted in the COVID-19 ARDS group. These findings suggest early pronation in the early exudative stage of ARDS can be more responsive to pronation. The structure and process of prone positioning protocols can be optimized by incorporating the stage of ARDS in conjunction with intubation days and to consider further diagnostics like CT chest imaging, ABG analysis, and ventilator mechanics for decision making. The current procedure for stopping prone positioning is with an improvement of oxygen in supine position $\geq$ 4 hours and a P/F ratio $\geq$ 150 mm Hg, $FiO_2 \leq 60\%$, PEEP $\leq$ 10 cm of water, or a P/F ratio > 20% of the relative ratio in supine position (Vollman et al., 2017). However, prolonged pronation greater than seven to ten days for P/F ratios $\leq$ 150 mm Hg in the fibroproliferative to fibrotic stages may not be necessarily beneficial. Furthermore, goals of care discussions would be imperative with clinicians and patient families based on clinical presentation. It was the overall aim for this comparative study to inform any improvements in nursing care for all cases of ARDS with guidance of the structure, process, and outcomes of Donabedian's model. The DNP project-lead found a potential benefit with an assertive pronation protocol in the early exudative phase of ARDS. The latter stages of ARDS and pronation are not as likely to be as beneficial due to lung fibrosis, prolonging ICU LOS and intubation days. This can lead to further risks including pressure injuries for patients, physical and psychological injury to front line ICU health care professionals. These outcomes are in accordance with previous RCTs, and current available literature of COVID-19 ARDS. It was found that there is an oxygenation benefit to pronating early in the first week of intubation. Therefore, a proactive pronation protocol is recommended in the early exudative stages of ARDS versus the fibroproliferative, and fibrotic stages.

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Table 1
Table of Evidence

CITATION	PURPOSE	SAMPLE	METHODS	RESULTS	DISCUSSION, LIMITATIONS OF FINDINGS
Fernandez et al. (2008). Prone positioning in acute respiratory distress syndrome: A multicenter randomized clinical trial. *Intensive Care Medicine, 34, 1487-14.* Doi:10.1007/s00134-008-1119-3	Prone positioning may be beneficial if started early and continuously	N=40 -19 supine -21 prone Age: -55.3 ± 14.6 supine -53.9 ± 17.9 prone Female: -31% supine -43% prone P/F ratio: -234 ± 85 vs 159 ± 73 on Day 3	Randomized trial Primary outcome was survival at 60 days Randomized within 48 hours with ≥ 20 hours per day of pronation Secondary outcomes was MV duration and length of stay in the ICU Two-way ANOVA Independent variable (IV): -prone positioning (PP) Dependent variable (DV): -Survival, Severity score, arterial blood gas, SOFA, MV duration, and ICU LOS	Day 3 of pronation were statistically significant -234 ± 85 vs. 159 ± 78, prone and supine groups, respectively, p = 0.009 -15% reduction in mortality in prone groups. Not statistically significant -ICU LOS 14.7 ± 9.7 vs 17.5 ± 16.1, prone and supine groups, respectively, p = 0.5 -Mechanical ventilation days 11.9 ± 9.2 vs. 15.7 ± 16.9, prone and supine groups, respectively, p = 0.5	-The trial was stopped early due to low recruitment -A possible survival advantage with early pronation and continuously. Future trials with greater financial support can be designed -Findings can add to meta-analysis of pronation literature to evaluate its effect on outcomes -Lack of efficacy of late pronation for rescue treatment

Guerin et al. (2013). Prone positioning in severe acute respiratory distress syndrome. *New England Journal of Medicine. 368,* pp. 2159 – 2168. Doi:10.1056/NEJMoa1214103	To evaluate outcomes of prone positioning in severe ARDS patients how this impacts mortality	N = 466 237 prone group 229 supine group Severe ARDS Multicenter trial of 26 ICUs in France and Spain that have been previously experienced with prone positioning for five years Main cause of ARDS was pneumonia, influenza A (H1N1) Randomized controlled trial	Severe ARDS with Fi02 < 150 mmHg, Fi02 ≥ 60%, PEEP ≥ 5 cm H20, TV of 6 ml per KG of predicted body weight Chi-square test, Fisher's exact test, and ANOVA Survival rates analyzed by Kaplan-Meier and log-rank test IV: prone positioning for 16 hours DV: Mortality at day 28, day 90, successful extubation rates, time to extubation, ICU length of stay, complications, tracheostomy rates, ventilator settings, arterial blood gases, respiratory mechanics, use of noninvasive ventilation, and number of free days from organ dysfunction.	28-day mortality rate 16% in prone group and 32.8% in supine group (P < 0.001) 90-day mortality rate 23.6% in prone groups and 41% in supine (P < 0.001) ICU length of stay in survivors were 24 ± 22 days in prone groups compared to 26 ± 27 days in supine groups (P < 0.87) In non-survivors, ICU length of stay 21 ± 20 days vs. 18 ± 15 days, prone and supine, respectively (P< 0.87) P/F ratios statistically significant in day 3 and day 5 Mean duration was 17 ± 3 hrs	Prone position in severe ARDS is efficacious in decreasing 28-day and 90-day mortality rates The low rates of complications associated with prone positioning may not be generalizable due to the high experience levels of nurses in providing pronation Incidence of complications were not significant between groups as cardiac arrest were more prevalent in supine group Statistical imbalance including baseline SOFA score, vasoactive medications, and neuromuscular blockers that can provide variation in results Prone positioning can benefit severe ARDS patients with early and long durations of pronation sessions.

Taccone et al. (2009). Prone positioning in patients with moderate and severe acute respiratory distress syndrome: A randomized controlled trial, 18(302), 1977-1984. Doi:10.1001/jama.2009.1614	To analyze outcomes of prone positioning with ARDS patients with moderate to severe hypoxemia	N = 342 Supine: 174 Prone: 168 -moderate ($Pa0_2/Fi0_2$ 100 to 200 mmHg): N=192 -severe ($Pa0_2/Fi0_2 < 100$ mmHg): N=150 Age: 60 (entire population mean) Gender: women (98%) P/F ratio mean entire population: 113	Randomized controlled trial. Physiological variables recorded at 12 hour intervals in the morning. Primary outcomes was mortality and the cause assessed at the 28th day. Secondary outcomes was at ICU discharge and six months, SOFA scores at 28 days, and ventilator free days. Pronation utilizing Rotoprone beds in 20 ICUs compared to 5 ICUs with manual procedure Prone duration 20 hrs / day T-tests, chi-square tests, Wilcoxon-Mann-Whitney tests. 2-factor analysis of variance, Kaplan-Meier curves IV: Prone positioning DV: Mortality at 28 days. Mortality data at discharge and 6 months, SOFA scores at 28 days, and ventilator free days.	Mean of 8.4 cycles of pronation at 18 hours per session. 28-day mortality rate was 52% compared to 57% in prone and supine groups, respectively (P = 0.72). ICU mortality rate was 64% compared to 73%, respectively (P = 0.47) 6-month mortality was 79% compared to 91% ($p = 0.33$) There were no ventilator free days Duration of mechanical ventilation in 28 days in survivors and non-survivors was 25 days compared to 19 days, respectively (P = 0.12) ICU length of stay median 17.5 days and 16 days, respectively (P = 0.17) Prolonged periods of pronation not associated with survival advantage. Prone duration 18 ± 4 hours per day Limitations include the selection of homogeneous patients due to standardization of PEEP between 5 to 10 cm of water. Severe hypoxemia patients had greater mortality rates with lower $Pa0_2$, $PaC0_2$, increased minute ventilation. There was a 72 hour period of enrollment that questions if earlier intervention can produce better outcomes. Underpowered study and mortality difference below 15% is not detected in 342 patients analyzed

Guerin et al. (2004). Effects of systematic prone positioning in hypoxemic acute respiratory failure. A randomized controlled trial.	To determine whether pronation improves mortality	N = 791 -413 prone -378 supine Multi-center, unblinded controlled trial Prone duration for 8 hours per day 12-24 hr stabilization period prior to intervention Prone: 62.0(15.7) yrs Supine: 62.5(14.7) yrs Prone: BMI: 26.2(6.1) Supine: BMI: 26.1(6.2) P/F ratio < 300 mmHg	Unblinded randomized trial Mean (SD) and median (SD) 2 groups using Pearson chi-square or Fisher exact test, *t* test, and Mann-Whitney test. Survival analyzed through Kaplan-Meier method and compared with by log-rank test SPSS version 11.0 for Windows IV: Prone positioning DV: -28 day Mortality -90 day mortality -P/F ratio -PEEP, VT, Fi02 -MV duration	MV duration Prone: 13.7 (7.8) days Supine: 14.1 (8.6) ICU LOS Prone: 26.6 (29.6) Supine: 24.5 (21.9); p=.35 Intubation to successful extubation: -16.9 (11.4) Pressure sores: -Prone: 208 -Supine: 157	Early pronation did not improve mortality Prone positioning cycle 4.1 (4.7) days for 8.6 (6.6) hours Pronation duration was a median 8 hours Pressure sores higher in prone groups Oxygenation with pronation improved from day 1 through day 7 (P < .001)

Gattinoni et al. (2001). Effect of prone positioning on the survival of patients with acute respiratory failure. *The New England Journal of Medicine, 345,* 568-573. Doi:10.1056/NEJMoa010043.	To evaluate if prone positioning has a survival benefit in patients with acute lung injury or ARDS. P/F ratio inclusion criteria: P/F ratio ≤ 200 mmHg with PEEP of 5 cm of water, and P/F ratio ≤ 300 mmHg with PEEP of 10 cm of water	N = 304 -prone: 152 -supine:152 Age (yr) -prone: 59 -supine: 57 Female (%) -prone: 34.2 -supine 25 Acute lung injury (%) -prone: 5.3 -supine: 6.6 ARDS (%) -prone: 94.7 -supine 93.4	No significant difference in mortality rate at 21.1% and 25% in prone and supine groups. Prone groups average duration was 7.0 ± 1.8 hours per day. Mean 4.6 ± 0.9 people to pronate P/F ratio increased 63 ± 66.8 vs. 44.6 ± 68, P = 0.02) Frequent adverse effects were increased sedation, urgent suctioning to clear airway, and facial edema. Unintentional extubation occurring 4 of 721 maneuvers of pronation.	Prone positioning can improve arterial oxygenation. Benefit may be with severe hypoxemia with P/F ratio ≤ 100 mmHg. Post hoc analysis found a need to have a future trial to evaluate prone positioning with severe ARDS. Routine use of prone positioning is not Recommended. No extubation data recorded. Small sample size, staff limitations and missed pronation cycles totaling 91 and non-compliance in 41 patients in ten days of evaluation. ICU mortality was 58% in supine groups compared to 43% in prone (*p*=0.12) There was a decrease in mortality rates with 15% absolute and 25% relative decrease in ICU mortality in prone groups compared to supine

Mancebo et al. (2006). A multicenter trial of prolonged prone ventilation in severe acute respiratory distress. *American Journal of Respiratory and Critical Care Medicine, 173*(11), 1233-1239. Doi:10.1165/rccm.200503-353OC.	To determine if there is a mortality benefit with earlier and longer prone positioning	N = 136 Prone positioning average 17 hrs Duration for 10 days Age (yr) -Prone: 54±17 -Supine 54±16 Gender (M/F) -Prone: 44/32 -Supine: 42/18 Day 2 P/F ratio: -Prone: 218 ± 85 mmHg -Supine: 171 ± 85 (P=0.002) Day 4 P/F ratio: -Prone: 215 ± 73 mmHg -Supine: 176 ± 72 mmHg (P=0.005)	Complications noted in 14 patients including dislodgement of swan ganz, cardiac arrest, conjunctival hemorrhage, pressure ulcers in two patients, and facial, limb, thorax edema	Post hoc analysis determined the subset of patients who benefited from pronation should be cautiously interpreted Limitations are the small sample size and underpowered analysis leading to the cessation of the study Prolonged pronation is safe and may provide a mortality benefit if instituted early ICU LOS -Prone: 20.5±18.2 -Supine: 19.1±23.1 (0.70) Significant results on day 2 and day 4 of pronation

Shelhamer et al. (2021). Prone positioning in moderate to severe acute respiratory distress syndrome due to COVID-19: A cohort study and analysis of physiology. *Journal of Intensive Care Medicine, 36*(2), 241-252. Doi:10.1177/0885066620980399	To determine if prone positioning compliments COVID-19 therapy	N = 335 -62 prone -199 non prone -74 excluded Single center level 1 trauma hospital in South Bronx, New York City Prone duration mean = 14 hours Males = 79% Females = 21% Age: 68.5 yrs BMI: 29.3 Complications: = 34 (8.8%)	A single center retrospective study Descriptive statistics Fine-Gray models Standard regression adjustment Linear mixed models IV: Prone positioning DV: in-hospital mortality and physiological parameters in prone and supine position Physiological parameters: -oxygenation index -oxygenation saturation index (OSI) -Pa02:Fi02 (P/F) -Sp02:Fi02 (SFR)	Median ICU length of stay 16 days Mortality reduction in 40% Days 1-3 significant increase in (OSI) with 21.3% improvement (P<0.01) Days 4-7 with significant effect. net increase of 57 mmHg (15.1% improvement) (P/F) (P<0.001)	Interdisciplinary pronation teams are effective and safe with utilization of a training program and standardization. Days 1-3, 4-7 with significant oxygenation improvement with pronation Suggests longer duration of pronation benefits oxygenation with a minimum of 4 days of prone positioning Extends survival Staff education and pronation teams are important

Doussot et al. (2020). Prone positioning for severe acute respiratory distress syndrome in COVID-19 patients by a dedication team. *Annals of Surgery,* 272(6), e311-315. Doi:10.1097/SLA.0000000000004265	To evaluate if standardized pronation protocols and training programs can optimize non-experienced health care workers in safely administering prone procedure in the ICU.	N = 67 Tertiary regional university hospital Prone duration mean = 14 hours Males = 79% Females = 21% Age: 68.5 yrs BMI: 29.3 Complications: = 34 (8.8%)	Prospective cohort study Independent *t* test or Mann-Whitney *U* test Chi-square test or Fisher exact test IV: Prone positioning with a team DV: -Duration of ICU stay -Median number of PP -Pre & Post PP oxygenation	Median ICU length of stay 16 days Mortality rate 15% (n = 10) Complications were 8.8% (n = 34) 69 (72.6%) of respondents reported pronation training to be helpful 8 healthcare workers had back pain 2 had joint pain 1 had anxiety Total amount of workers had 11 (12%) pronation related symptoms.	Interdisciplinary pronation teams are effective and safe with utilization of a training program and standardization.

Appendix

Appendix 1: Inclusion and Exclusion Criteria