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Assessing the Neurological Sequelae of COVID-19 and Acute Respiratory Distress Syndrome

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Abstract and Keywords

COVID-19 infection leading to acute respiratory distress syndrome (ARDS) has been associated with impaired neurocognitive function and is known to increase the risk for endothelial dysfunction and coagulopathy affecting the vasculature of the brain. Recent studies have reported a higher concentration of cytokine and glutamate receptors along white matter tracts which may increase susceptibility to inflammatory-induced damage, further affected by hypoxemia due to direct and indirect lung damage. We conducted a systematic review and meta-analysis which suggests that the combination of ARDS and COVID-19 doubles the risk of developing intracranial hemorrhage and increases vulnerability to cerebral white matter injury as opposed to ARDS of other causes. Given the findings of the review, we then assess image analysis methods to detect these injuries, particularly white matter hyperintensities (WMH). Although various deep learning techniques have been proposed to automatically quantify WMH, the influence of image preprocessing steps on segmentation accuracy has been underexplored. We examine the impact of five intensity normalization methods on deep learning segmentation accuracy, emphasizing the importance of careful consideration for WMH analysis in COVID-19 ARDS populations. Further exploration of intensity normalization approaches using the Neuro-SAVE ICU data is underway to determine the optimal method for WMH analysis.

Magnetic Resonance Imaging, Critical Illness, COVID-19, White Matter Hyperintensities, Neuroinflammation

Summary for Lay Audience

Acute Respiratory Distress Syndrome (ARDS) is a condition resulting from severe lung injury. The diagnostic criteria for ARDS, known as the 'Berlin definition,' include the timing of respiratory symptoms onset, low oxygen levels despite oxygen therapy, and fluid accumulation in the lungs leading to respiratory failure. This fluid buildup can damage the pulmonary surfactant, which prevents lung collapse. Inflammatory mediators called cytokines released by immune cells in the lungs can trigger a secondary inflammatory response in the brain, involving microglia activation. In some cases, this response can become excessive, damaging blood vessels and neurons, which can be observed through brain imaging techniques like MRI. COVID-19 infection is the focus of this thesis as a potential cause of ARDS. The SARS-CoV-2 virus responsible for COVID-19 enters the body through ACE-2 receptors, which are concentrated in the lungs. The virus destroys these receptors, leading to an immune response that further damages lung cells. Severe infections can result in ARDS, and there is evidence suggesting that COVID-19-related ARDS may increase the frequency of brain injuries, particularly affecting white matter. Such injuries pose a higher risk of disability and mortality for patients.

The thesis consists of two parts. The first part reviews previous research on brain injuries in ARDS, including their frequencies and associated risks. The second part focuses on analyzing MRI data, specifically when dealing with low-quality clinical data. The findings indicate that COVID-19 ARDS patients are twice as likely to experience brain hemorrhages compared to other causes of ARDS. Additionally, COVID-19 may specifically impact white matter tracts in the brain. To improve analysis efficiency and enhance understanding, the thesis proposes the use of deep learning techniques for automatic detection of white matter lesions. Further research is necessary to fully understand the impact of COVID-19 ARDS on the brain. This knowledge will be crucial for scientists and healthcare systems in developing and providing support to COVID-19 ARDS survivors.

Co-Authorship Statement

Chapter 2 of this thesis was adapted from "Spectrum of Brain Injury in COVID-19 Acute Respiratory Distress Syndrome (ARDS): A Systematic Review," a manuscript submitted to Lancet Neurology and co-authored by Dr. Michael T. Jurkiewicz, Dr. Paulien Moyaert, Jennifer Chen, Alla Iansavichene, Emily Dawson, Dr. Angela Jerath, Dr. Marat Slessarev, and Dr. Udunna C. Anazodo. Dr. Michael T. Jurkiewicz conceptualized the review. Alla Iansavichene identified appropriate databases for searching, created the initial literature search and collected study articles. Jennifer Chen and Rachel Wagner contributed to assessing articles for eligibility. Dr. Udunna C Anazodo, Emily Dawson and Rachel Wagner performed data analysis. Dr. Paulien Moyaert, Dr. Udunna C Anazodo, Dr. Marat Slessarev, Emily Dawson, and Rachel Wagner assisted in the preparation of figures and tables. Dr. Udunna C Anazodo, Dr. Michael T Jurkiewicz, Dr. Angela Jerath, contributed to the supervision of the review. Rachel Wagner, Dr. Udunna C Anazodo, Dr. Marat Slessarev, Dr. Michael T Jurkiewicz, Dr. Angela Jerath, and Dr. Paulien Moyaert contributed to the editing of the protocol and manuscript and writing of the original draft and revisions. Raymond Confidence and Linshan Liu contributed to data analysis of the MRI scans utilised in chapter 3. Dr. Michael T Jurkiewicz and Dr. Pavlo Ohorodnyk generated ground truth annotations for the MRI data included in Chapter 3. Dr. Udunna Anazodo conceptualized the study described in chapter 3. All co-authors participated in review and editing of the manuscript.

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List of Abbreviations, Symbols, Nomenclature

AAL	Automatic Anatomical Labelling
ACE-2	Angiotensin-Converting Enzyme 2
AD	Alzheimer's Disease
APACHE II	Acute Physiology and Chronic Health Evaluation
ARDS	Acute Respiratory Distress Syndrome
BAL	Bronchoalveolar Lavage
BBB	Blood-Brain Barrier
COPD	Chronic Obstructive Pulmonary Disease
CM	Cerebral Microbleeds
CSVD	Cerebral Small Vessel Disease
CT	Computed Tomography
CVT	Cerebral Venous Thrombosis
DBP	Diastolic Blood Pressure
DICOM	Digital Imaging and Communications in Medicine
DAD	Diffuse Alveolar Damage
DTI	Diffusion Tensor Imaging
DWI	Diffusion-Weighted Imaging
ECMO	Extracorporeal Membrane Oxygenation
EDH	Epidural Hemorrhage

ESNR	European Society of Neuroradiology
FLAIR	Fluid Attenuated Inversion Recovery
ICH	Intracranial Hemorrhage
ICTRP	International Clinical Trials Registry Platform
ICU	Intensive Care Unit
KDE	Kernel Density Estimation
MAP	Mean Arterial Pressure
MERS	Middle East Respiratory Syndrome
MeSH	Medical Subject Headings
MOF	Major Organ Failure
MP-RAGE	Magnetization-Prepared Rapid Gradient Echo
MRI	Magnetic Resonance Imaging
NIFTI	Neuroimaging Informatics Technology Initiative
NAWM	Normal Appearing White Matter
NOS	Newcastle-Ottawa Scale
PaO_2/FiO_2	Ratio of Arterial O_2 Partial Pressure to Inspired O_2 Fraction in mm Hg
PCR	Polymerase Chain Reaction
PE	Pulmonary Embolism
PET	Positron Emission Tomography

PROSPERO	Prospective Register of Ongoing Systematic Reviews
PSCI	Post-Stroke Mild Cognitive Impairment
PTSD	Post-Traumatic Stress Disorder
RAS	Renin-Angiotensin System
RASS	Richmond Agitation Sedation Scale
ROI	Region Of Interest
SAPS II	Simplified Acute Physiology Score
SARS	Severe Acute Respiratory Syndrome
SARS-COV-2	Severe Acute Respiratory Syndrome Coronavirus-2
SBP	Systolic Blood Pressure
SD	Standard Deviation
SOFA	Sequential Organ Failure Assessment
SAH	Subarachnoid Hemorrhage
SDH	Subdural Hemorrhage
SWI	Susceptibility Weighted Image
T1W1	T1-Weighted Image
VILI	Ventilator-Induced Lung Injury
WM	White Matter
WMH	White Matter Hyperintensity

WHO	World Health Organization
3D	Three-Dimensional

Chapter 1

1.1 ARDS Etiology and Pathogenesis

Acute respiratory distress syndrome (ARDS) is a severe form of lung injury precipitated by irreparable damage to the alveolar-capillary membrane lining the lungs, impairing systemic oxygenation circulation. The currently accepted diagnostic criteria for ARDS follow the 'Berlin definition', (ARDS Definition Task Force, 2012) including the sudden onset of impaired oxygenation (defined as the ratio of arterial oxygen partial pressure to inspired oxygen fraction in mm Hg [PaO_2/FiO_2 ratio] equal to or lesser than 300 mm Hg) and the presence of fluid buildup in the alveoli, evidenced by chest imaging. ARDS is further classified into three categories based on the severity of hypoxemia: mild (PaO_2/FiO_2 between 200-300 mm Hg), moderate (PaO_2/FiO_2 between 100-200 mm Hg), and severe (PaO_2/FiO_2 less than 100 mm Hg) (Huppert et al., 2019). It is estimated that ARDS affects between 10% to 15% of all patients admitted to the intensive care unit (ICU) globally and is one of the leading causes of mortality in critical illness, causing death in up to 40% of diagnosed patients (Bellani et al., 2016; Sharma et al., 2010). ARDS can be caused by either direct lung injury (e.g. pneumonia, aspiration or inhalation) or through indirect lung injury (eg. sepsis or pancreatitis). The pathogenesis of ARDS involves a number of interrelated factors, including inflammatory mediators, endothelial dysfunction, and coagulopathy. ARDS most commonly occurs in cases of pneumonia, sepsis, aspiration of stomach or oral contents, blunt trauma, and, less commonly, as a result of pancreatitis, drug overdoses, secondary drowning, hemorrhagic shock or smoke inhalation (often in combination with burn injuries) (Huppert et al., 2019).

ARDS is known to progress through three consecutive phases: exudative, proliferative, and fibrotic. The exudative phase involves fluid buildup in the alveoli with proteinaceous fluid, neutrophil activation, and inflammatory cytokine release. In the proliferative phase, lung repair mechanisms are activated, including fibroblast proliferation and deposition of extracellular matrix. During the fibrotic phase, lung tissue becomes scarred, resulting in chronic lung damage (Marshall et al., 1998; Matthay et al., 2019; Ware & Matthay 2000). The development of ARDS begins with the initial injury to the alveolar-capillary membrane lining the lungs, subsequently causing a local inflammatory response. Inflammatory insults can cause accumulation of protein-rich edema fluid

in the alveoli, leading to impaired gas exchange and hypoxemia. Alveolar macrophages lining the lungs recruit neutrophils and circulating macrophages which produce inflammatory mediators such as proteases, reactive oxygen species, and cytokines. Inflammatory cytokines such as Interleukin-1β (IL-1β), Tumour Necrosis Factor-α (TNF-α), Interleukin-6 (IL-6), and Interkeulin-8 (IL-8) are known to be elevated both in bronchoalveolar lavage (BAL) fluid and circulating plasma in ARDS patients, indicating a systemic inflammatory response (Matthay et al., 2019; Shankar-Hari et al., 2019). As this immune response is propagated, alveolar type 2 epithelial cells are damaged causing functional impairment and cell death. Alveolar type 2 cells are responsible for the production of pulmonary surfactant and aid in the control of fluid levels in the lungs, damage to which leads to loss of regulation and subsequently, alveolar fluid buildup characteristic of ARDS (Matthay et al., 2019; Ware & Matthay, 2000). As inflammatory mediators continue to be released, the response is exacerbated by the activation of coagulopathic response, leading to the formation of microthrombi in the lung blood vessels, increasing their permeability and function, further impairing the exchange of oxygen from the lungs and increasing fluid buildup. This process is self-propagating, as the damage to these epithelial cells causes functional impairment in epithelial sodium channels, further contributing to impaired alveolar fluid clearance. As the pathogenesis of ARDS progresses, the fluid buildup and impairment of oxygen exchange can lead to severe hypoxemia and respiratory failure (Matthay et al., 2019; Ware & Matthay 2000).

1.2 Interventions and Therapies for ARDS

The treatment of ARDS focuses on identifying and targeting the underlying cause of the initial lung injury, maintaining organ function, and treating symptoms and consequences of lung injury, such as hypoxemia, respiratory failure, and sepsis, generally using antibiotics, antivirals, and mechanical ventilation. ARDS patients typically present with a condition known as “baby lung,” in which there is a smaller-than-normal portion of the lungs which remain oxygen-filled due to the buildup of fluid. Positive end-expiratory pressure (PEEP) is often used to avoid placing additional pressure on the lungs which may cause Ventilator-Induced Lung Injury (VILI) (Matthay et al, 2019). Physicians typically use a mechanical ventilation strategy called protective lung ventilation that utilizes low tidal volumes to attenuate VILI. Additional treatments for patients may include prone positioning aimed to improve oxygenation, fluid restriction, adequate nutrition, and pharmacologic treatment (Fan et al., 2017; Matthay et al, 2019; Williams et al., 2021). Several

medications have been studied for the treatment of ARDS, including corticosteroids, inhaled nitric oxide, and surfactant replacement therapy. However, their use remains controversial, and no specific pharmacologic therapy has been shown to be consistently effective in treating ARDS. In the most severely ill patients for whom mechanical ventilation has failed, extracorporeal membrane oxygenation (ECMO) may be used. ECMO involves surgical implementation of a circuit that oxygenates and removes carbon dioxide from the patient's blood, allowing the lungs to recover from the inflammation and injury. Research indicates ECMO improved survival in these patients, with 60-day mortality rates of 35% in the ECMO group compared to 46% in the conventional ventilation group. However, ECMO can cause complications during treatment, including brain damage, bleeding, infections, and vascular injury (Combes et al., 2018; Matthay et al., 2019).

1.3 Long-Term Neurocognitive Impairment and Neuroimaging in ARDS

While ARDS initially impacts the lungs, it is known to exert multi-organ impact as the inflammatory response propagates. In a study of 29,144 ICU patients, ARDS was found to represent 10.4% of total admissions with an age range from 60.9 to 62.1. Participants were 38% female and presented with a range of comorbidities, including chronic obstructive pulmonary disease (COPD) (21.7%), diabetes (21.7%), immuno-incompetence (21.2%), chronic cardiac failure (10.4%), chronic renal failure (10.1%), active neoplasm (8.5%), and hematological disease (4.7%). The brain is among the targets of ARDS pathogenesis, ARDS has been associated with an increased risk of long-term neurocognitive impairment, including deficits in memory, attention, and executive function across the spectrum of severity (Pandharipande et al., 2013; Sasannejad et al., 2019). It is thought that persistent neurocognitive issues seen in these patients may be a result of hypoxia, inflammation, oxidative stress, for endothelial dysfunction during illness, which increases the likelihood of developing psychiatric conditions such as delirium, anxiety, post-traumatic stress disorder (PTSD) and depression, the incidence of which are elevated in ARDS patients (Jackson et al., 2014; Karanikas et al., 2021; Mart et al., 2020; Matthay et al., 2019). A study conducted by Girard et al. (2010) indicated prevalence of cognitive impairment in 99 ARDS survivors to be 62% at 3 months after discharge, with deficits in attention and executive function (Girard et al., 2010). This impact is known to be persistent, with a prospective cohort study of ARDS survivors finding that 40% had cognitive impairment 3 months after hospital discharge

(Pandharipande et al., 2013). In a systematic review and meta-analysis of ARDS, 47% of patients were indicated as having deficits in memory, attention, and executive function. The long-term functional disability in ARDS survivors is associated with decreased quality of life and increased healthcare costs (Hopkins et al., 2005; Pun et al., 2019).

While neuroimaging research remains limited in ARDS, there is known to be an association between ARDS and the occurrence of brain injury. Magnetic Resonance Imaging (MRI) studies in ARDS patients have shown a spectrum of injuries, including cerebral edema, diffuse axonal injury, and white matter abnormalities. A recent review of animal studies of ARDS pathogenesis indicated statistically significant, increased presence of neuroinflammation and neuronal damage within the hippocampus of the rat animal models. In addition, they found that 82-86% of ARDS survivors present with brain injury or impaired neurological function, most commonly hemorrhagic stroke, ischemic stroke, and cerebral edema (Huang et al. 2021). Diffusion tensor imaging (DTI) studies have shown evidence of diffuse axonal injury in ARDS patients, particularly in those with longer duration of mechanical ventilation, which may suggest increased risk for developing brain injuries due to severity of illness. Other neuroimaging studies in ARDS patients have shown evidence of decreased cerebral blood flow and altered cerebral metabolism, suggesting that the brain may be impacted by the systemic effects of the disease (Chacon-Aponte et al., 2022; Contant et al, 2001; Hopkins et al, 2016; Jackson et al, 2009; Morandi et al. 2012; Sonneville et al. 2013).

1.4 COVID-19 Etiology and Pathogenesis

The Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) virus was first reported in late 2019 and was the cause of the COVID-19 pandemic following its rapid spread around the world. SARS-CoV-2 is a member of the family of viruses known as coronaviruses, which can cause respiratory illnesses ranging from the common cold to more severe illnesses such as SARS (Severe Acute Respiratory Syndrome) and MERS (Middle East Respiratory Syndrome). The virus is transmitted through respiratory droplets or by touching infected surfaces. The virus primarily infects the respiratory tract, and its symptoms can range from mild to severe, including fever, cough, shortness of breath, fatigue, body aches, and loss of taste or smell (Centers for Disease Control and Prevention, 2021). The SARS-CoV-2 virus enters host cells by binding to the angiotensin-converting enzyme 2 (ACE2) receptor on the surface of lung epithelial cells. The virus

then replicates and causes damage to the lung tissue, leading to an inflammatory response that can result in severe lung injury. In patients with COVID-19, circulating levels of ACE-2 were found to be increased and associated with viral load and severity of lung injury. In its normal function, ACE-2 hydrolyzes its binding substrate, Angiotensin-II, which exerts anti-inflammatory and bronchodilatory effects. The internalization of ACE-2 receptors in COVID-19 infection downregulates ACE2 expression and increases circulating ACE-2, which may be involved in multiple organ injury in COVID-19 (Huppert et al., 2019; Matthay et al., 2019; Ni et al., 2020; Ziehr et al. 2020) (see Figure 1.1). SARS-CoV-2 may pass across the respiratory epithelium to systemic circulation, causing the release of inflammatory cytokines and affecting other organs such as the brain. Such inflammation is thought to promote hypercoagulability and endothelial dysfunction in COVID-19 (Otifi et al. 2022). Consequently, cytokine release systemically causes further injury by disrupting tight endothelial–epithelial barriers, further suggesting patients with severe COVID-19 infection are more likely than non-severe to present with multiple organ involvement, such as serious liver, kidney, and skeletal muscle damage (Mao et al. 2020; Otifi et al., 2022). Cytokines can cross the blood-brain barrier (BBB), which can induce activation of the brain's tissue resident microglia, potentially resulting in a hyperactive neuroinflammatory response. This in combination with the decreased platelet levels in damaged lungs, may predispose patients for developing vascular injuries, especially in the setting of anticoagulant or antithrombotic medications. Notably, one study reported lower platelet counts in COVID-19 patients presenting with central nervous system (CNS) symptoms compared to those without CNS involvement, which may relate to increased risk for acute cerebrovascular disease in such patients (Hernandez-Parra, 2023; Mao et al, 2020; Otifi et al., 2022; Wool et al., 2020).

1.5 Interventions and Therapies for COVID-19

Current treatments for COVID-19 vary depending on illness severity and are still being researched, however, antiviral therapy, immunotherapy, and adjunctive therapies have been used. The most commonly taken medications include remdesivir, an RNA polymerase inhibitor, which has been shown to lessen the time to recovery in hospitalized patients with COVID-19; corticosteroids, which have been shown to reduce the need for mechanical ventilation; and tocilizumab, an interleukin-6 inhibitor (Beigel et al., 2020; Hong et al., 2022; Sanders et al., 2020; Salama et al., 2021; Sterne et al., 2020). Adjunctive therapies such as plasma transfusions and antibodies have

also been studied for the treatment of COVID-19, which may reduce hospitalizations in patients with mild to moderate COVID-19 infection (Gottlieb et al., 2021).

1.6 Tropism and Multi-Organ Impact in COVID-19

While the lungs serve as the initial site of infection, COVID-19 can infect many different organs in the body. The tropism of SARS-CoV-2 is extensive and dependent on the concentration of ACE2 receptors and is thought to underlie the development of multi-organ impact of COVID-19. COVID-19 infection can replicate in gastrointestinal cells and can disrupt the gut microbiome, leading to dysbiosis and inflammation and gastrointestinal symptoms, such as nausea, vomiting, and diarrhea (Tian et al. 2020). The virus can additionally infect cardiac cells due to the presence of ACE-2 receptors lining cardiac epithelium, further increasing risk for the formation of coagulopathy, prothrombotic state and increased risk of cardiovascular events such as myocarditis, arrhythmias, and thromboembolic events (Clerkin et al. 2020). Renal complications, such as acute kidney injury, have been reported in some COVID-19 patients, particularly those with severe disease (Batlle et al. 2020). The virus may directly infect renal cells, and its effects on the immune system and coagulation system can lead to renal injury and dysfunction. Finally, COVID-19 can have a significant impact on the immune system itself, with reports of lymphopenia and dysfunction of T and B cells. This may contribute to a more severe and prolonged course of disease, as well as increased susceptibility to secondary infections (Chen et al. 2020).

1.7 Neurological Evidence from Past Coronavirus Pandemics

Patients experiencing severe COVID-19 infection are likely to exhibit neurological symptoms such as dizziness, confusion, impaired consciousness, seizures, acute cerebrovascular disorders, and neurocognitive impairments. A recent cohort study indicated the estimated incidence of a neurological or psychiatric diagnosis in the following 6 months among 236,379 COVID-19 patients as 33-62% (Taquet et al. 2021). The massive transmission of SARS-CoV-2 globally suggests that a substantial number of survivors of infection precipitating critical illness may suffer from potential SARS-CoV-2-related neurological disorders. Besides respiratory tract infections, several other coronaviruses and other respiratory viruses have been associated with neurological clinical manifestations in patients with a severe occurrence of infection. SARS-CoV-2 attacks the lower parts of the human respiratory system as in MERS-CoV and SARS-CoV and binds to ACE-

2 receptors as is the case in SARS-CoV, to which it also shares a highly homologous sequence, presenting an important research opportunity (Abdelrahman et al., 2020; Davidson et al., 2020). While comparatively fewer studies were made of neurological associations during past coronavirus epidemics, neurological issues similar to those seen in COVID-19 patients have also been reported during past SARS and MERS outbreaks. In a study of 206 patients infected with SARS, 2.42% cases of acute cerebrovascular disease were observed, hypothesized to be related to hypercoagulability due to additional thrombotic complications (Umapathi, 2004). Another study of MERS patients further reported confusion and seizures in 25.7 and 8.6% of the participants, respectively (Saad et al. 2014). While neuroimaging data of past pandemics is limited, MRI scans of three MERS infected patients exhibiting neurological symptoms revealed bilateral hyperintense lesions in subcortical white matter regions of the frontal, temporal, and parietal lobes, as well as the corpus callosum (Arabi et al. 2015). While mechanisms remain unclear, previous animal studies have indicated that immunopathogenic response initiated with CoVs infections could lead to demyelinating processes either in the brain or in the spinal cord (Bakhtazad et a, 2021). Notably, there has been found to be greater vasculopathy, including thrombosis and endothelial cell injury in COVID-19 and the earlier SARS injury than with H1N1 influenza and ARDS (Ackermann et al, 2020) Although evidence in the literature supports the presence of neurological impact in SARS, MERS and COVID-19 infection, it remains difficult to ascertain how the different neurological features relate to the overall pathophysiology and whether it is the result of direct or indirect viral impact, or of characteristic features of comorbid ARDS, such as hypoxia, sepsis or multi-organ failure.

1.8 Long-Term Neurocognitive Impairment and Neuroimaging in COVID-19

There is evidence indicating SARS-CoV-2 infection may increase the likelihood for the development of neurological damage, even in the case of mild to moderate infection. Wang et al. (2022) reviewed medical records for 410,748 adults with a mean age of 73.7 with past COVID-19 infection and compared findings to 5,834,534 adults with a mean age of 73.0, without past infection. They found that older adults with COVID-19 were at significantly increased risk for novel diagnosis of Alzheimer's Disease (AD), indicating an overall risk of 0.68%, compared to 0.35% in the non-COVID-19 cohort. The risk for developing AD was highest in people aged >85 and in women. The COVID-19 cohort presented with higher prevalence of Hispanic and black

people and higher prevalence of adverse socioeconomic determinants of health. There is also evidence of persistent cognitive and neurological impairments in patients recovered from COVID-19, an effect which is seen in both mild and severe cases. A recent study of 478 COVID-19-positive individuals found that they performed worse on cognitive tests measuring reasoning, verbal abilities, processing speed, and overall cognitive performance compared to a normative sample. While better physical health was linked to better cognitive performance, with increased disease severity and older age being associated with decreased performance, cognition was also impaired in mild COVID-19 (Wild et al., 2023).

Neuroimaging studies in patients with mild to moderate COVID-19 have further revealed a range of brain abnormalities, implicating potential long-term neurocognitive impairments even in the context of mild infection. Neuroimaging studies of patients with severe infection have shown evidence of both ischemic and hemorrhagic strokes in COVID-19 patients, as well as brain atrophy, encephalitis, and meningitis, however, research is limited regarding brain injuries in mild to moderate COVID-19. In a multicenter study of hospitalized SARS-CoV-2 patients from 11 countries by Shahjouei et al. (2020), the pooled risk of stroke was 0.5%, the incidence of which was found to be independently predicted by mechanical ventilation and history of ischemic heart disease. The most commonly reported finding on neuroimaging in mild to moderate COVID-19 includes abnormalities in the olfactory bulb and tract, which may be related to the loss of sense of smell that is frequently reported in COVID-19 patients (Douaud et al. 2022). However, a recent cohort study conducted by Petersen et al. (2023) suggests increased risk of neurological damage following neuroimaging of unvaccinated people with past mild to moderate SARS-CoV-2 infection, a median of 289 days after acute infection, across various measurements of brain structure and function. Diffusion Weighted Imaging (DWI) on brain MRI demonstrated significant increases in extracellular free water content and elevation of mean diffusivity along white matter tracts, suggesting possible disruption to the microstructure, markers associated with immune activation and atrophy. The study authors further examined the complete white matter skeleton and observed mean diffusivity increases in 41.3% of the regions and free-water elevations in 38.3% of post-SARS-CoV-2 individuals. While all lobes were affected, mean diffusivity was particularly elevated in the white matter tracts. Interestingly, while white matter diffusion scores predicted past SARS-CoV-2 infection, outcomes from measures such as cortical thickness and

markers of cerebral small vessel disease were not significantly different between groups. This suggests that while mild to moderate SARS-CoV-2 infection is associated with microstructural white matter alterations, these changes may not contribute to diagnosable levels of brain injury on conventional clinical neuroimaging techniques.

Of additional concern, research indicates brain injury may not be limited to white matter tracts in mild to moderate COVID-19 (Douad et al. 2022). A recent study conducted by Douoad et al. (2022) investigated brain changes in 785 UK Biobank participants who tested positive for COVID-19 between two MRI scans, and found patients had a decrease in gray matter thickness, neuronal tissue damage in the olfactory cortex, as well as decrease in global brain size compared to 384 control group participants. Notably, these structural differences observed by the study authors were relatively small in magnitude at approximately 2% of the average initial value as compared to the annual longitudinal loss of around 0.2% to 0.3% of hippocampal volume in the average healthy person. Additionally, Douaud et al. (2022) found significant cognitive decline in the SARS-CoV-2-positive group between follow up time points which was found to be associated with increased atrophy in a cognitive region of the cerebellum.

1.9 COVID-19 ARDS Etiology and Pathogenesis

ARDS is increasingly recognized as a highly heterogeneous diagnosis, with current research suggesting classification into differing phenotypes, most commonly grouping patients as having developed ARDS through either direct or indirect lung injury. Pathologically, direct ARDS has been associated with significantly more alveolar collapse, fibrin deposition, and alveolar wall edema than indirect ARDS, indicating the two phenotypes may be pathophysiologically distinct (Bellani et al., 2016; Shaver et al, 2014). ARDS research has more recently further classified diagnoses on the basis of clinical characteristics, including severity, timing of symptom onset, risk factors, and varying responses to therapies. In one such study, patients with trauma-associated ARDS had significantly lower plasma levels of markers of epithelial and endothelial injury, but not markers of acute inflammation or coagulation (Calfee et al., 2007). During the course of the COVID-19 pandemic, severe SARS-CoV-2 infection emerged as a precipitating condition for the development of ARDS and has been postulated to constitute a distinct phenotype of ARDS due to its potentially unique clinical profile. While COVID-19 is primarily a respiratory illness, the virus can affect multiple organs throughout the body, leading to a wide range of clinical manifestations

and complications. While most patients present with mild respiratory illness, a recent cohort study reported that as many as 61-85% of ICU patients admitted due to severe coronavirus disease of 2019 (COVID-19) infection progress in the severity of their infection to meet the Berlin Criteria definition of ARDS (ARDS Definition Task Force, 2012; Gibson et al.,. 2020; Wu et al. 2020; Ziehr et al. 2020; El-Solh et al. 2021).

COVID-19 ARDS is caused by direct viral damage to the lungs during the course of COVID-19 infection, in which the alveolar and vascular endothelium cells lining the lungs expressing ACE-2 are damaged. COVID-19 ARDS is characterized by diffuse alveolar damage (DAD), further causing increased permeability of the lung tissue, accumulation of fluid and protein-rich exudate in the alveolar spaces, and impaired gas exchange. As the infection and subsequent inflammatory response propagate, there is increased cell death and damage to the alveolar-capillary barrier, further contributing to lung injury and exacerbating the damage caused by ARDS (Middleton et al., 2021). One prevalent theory underlying the damage caused in COVID-19 ARDS is the occurrence of a cytokine storm, characterized by an excessive release of inflammatory cytokines leading to increased vascular permeability and subsequent respiratory failure. It is also thought that activation of the renin-angiotensin-system (RAS), a system involved in blood pressure regulation, may be a source of injury in COVID-19 ARDS, which is a system involved in blood pressure regulation. The SARS-CoV-2 virus enters host cells via the ACE-2 receptor, a key impactor in the regulation of the RAS system, damage to which may lead to vasoconstriction, inflammation, and vascular permeability (Ni et al., 2020). A third hypothesized component to patterns of injury in COVID-19 ARDS is the formation of a prothrombotic state and endothelial dysfunction through activation of platelets. Occurrence of coagulopathic response and endothelial dysfunction in COVID-19 ARDS is thought to be due to direct viral infection in endothelial cells causing leakiness and cell death, hypoxemia due to lung damage and disrupted RAS system. Inflammatory cytokines causing systemic inflammatory response activating coagulation pathways and thrombosis are also thought to contribute the multi-organ impact seen in patients with COVID-19 ARDS (Connors & Levy, 2020; Matthay et al., 2019; Ni et al., 2020; Semeraro et al., 2021). A recent study of autopsied lungs from COVID-19 and H1N1 patients were compared to uninfected lungs and indicated the lungs from COVID-19 patients had increased presence of DAD, T-cell infection, endothelial injury, thrombosis, and increased angiogenesis compared to H1N1 and

healthy lungs, and had nine times the amount of microthrombi. Vascular angiogenesis distinguished COVID-19 pulmonary pathobiology from H1N1 patients. (Ackerman et al. 2020).

1.10 Interventions and Therapies for COVID-19 ARDS

Treatment for COVID-19 ARDS includes oxygenation and treating underlying complications, including mechanical ventilation, oxygen therapy, and prone positioning to improve oxygenation and lung function. In addition, pharmacologic agents such as corticosteroids, anticoagulants, and immunomodulators may be used to manage inflammation, coagulation, and immune dysregulation in patients with severe COVID-19 ARDS and focus on maintaining organ function (Siddiqi et al. 2020). Neurological complications are also increasingly recognized in COVID-19 ARDS patients, with reports of encephalitis, stroke, and seizures. The virus may directly infect neuronal cells and cause inflammation and immune-mediated damage to the central nervous system (Mao et al., 2020).

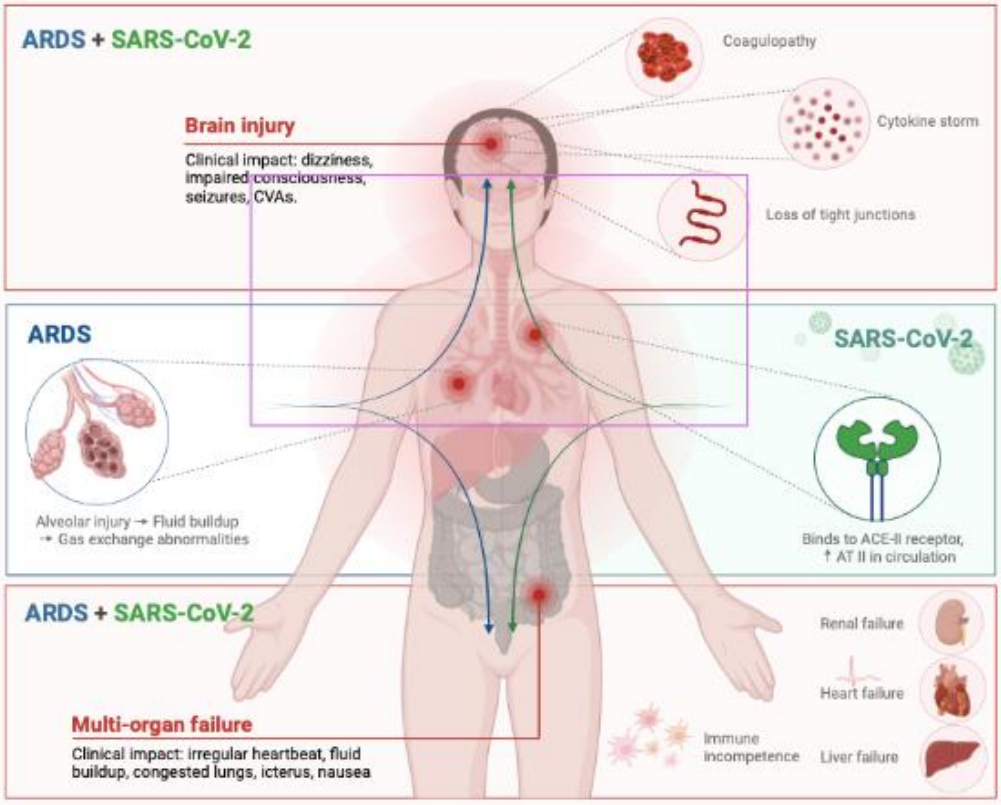
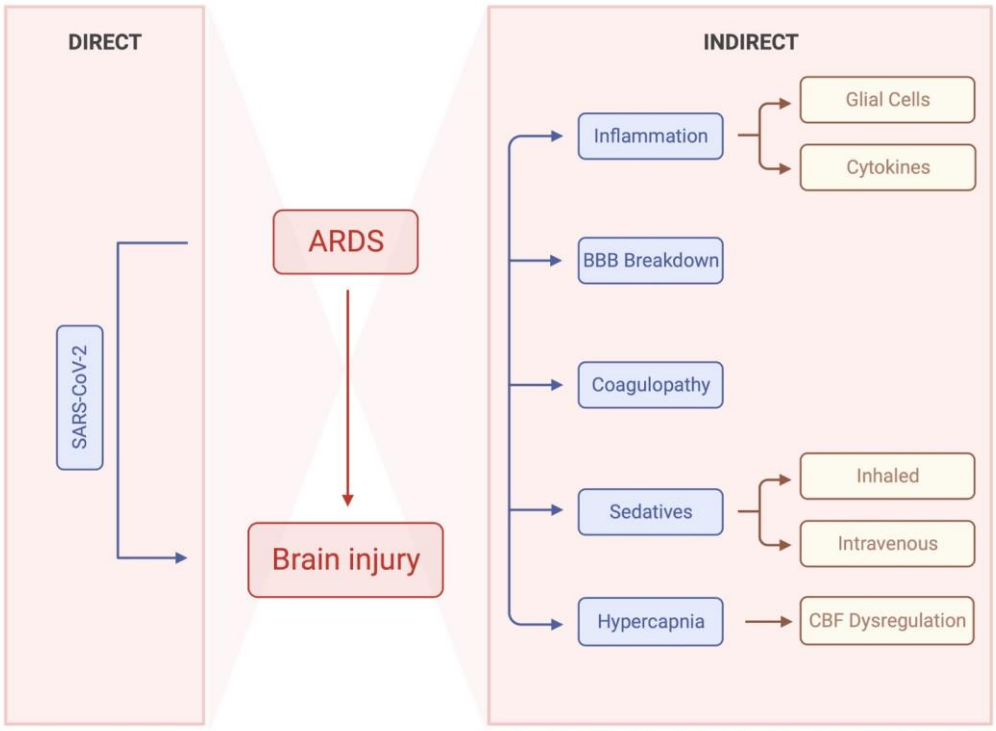


Figure 1.1: Postulated mechanisms of COVID-19 ARDS-mediated brain damage. The alveolus is depicted as injured by endothelial and epithelial injury, greater alveolar–

capillary permeability, alveolar edema, and recruitment of inflammatory cells. Activation of proinflammatory cytokine mediators propagate the injury and spillover into the circulation to cause systemic organ damage and dysfunction. SARS-CoV-2 viruses bind to angiotensin-converting enzyme 2, deactivating it and upregulating circulating angiotensin II, propagating lung injury and inflammatory response, leading to brain injury. Created with Biorender.com

1.11 Long-Term Neurocognitive Impairment and Neuroimaging in COVID-19 ARDS

Anatomical MRI data indicates patients with COVID-19 ARDS have a high prevalence of cerebrovascular disease, intracranial hemorrhage (ICH), microhemorrhages, and encephalopathy, and commonly present with long-term cognitive impairment which can persist for months to years following recovery (Bain et al. 2021; Huppert et al., 2019; Matthay et al., 2019; Shoskes et al., 2022). The pathophysiology underlying these complications is unclear but may relate to direct brain injury from the SARS-CoV-2 virus or from sequelae of associated hypoxia, ischemia, endothelial injury, or inflammation common in COVID-19 ARDS (see Figure 1.1 and Figure 1.2) (Bain et al. 2021; Huppert et al., 2019; Matthay et al., 2019; Shoskes et al., 2022). Furthermore, the prevalence and risk factors associated with neuroimaging findings vary between studies and imaging modalities. A recent review compared neuroimaging findings of mild and severe COVID-19 infection and found that patients with mild disease most commonly presented with abnormalities in the olfactory tract, followed by white matter abnormalities. In comparison, patients with severe disease presented more frequently with white matter abnormalities, and hemorrhagic stroke. Interestingly, both mild and severe COVID-19 infection showed similar levels of ischemic stroke, suggesting pathology unique to SARS-CoV-2 infection, potentially due to a coagulopathic response. Hemorrhagic strokes were more common in severe COVID-19 infections. While both mildly and severely infected patients showed brain injuries in the cerebral white matter, this was more frequently found in patients with severe infection (Pan et al. 2020).



1

Figure 1.2: Postulated mechanisms of ARDS-mediated brain damage through direct and indirect pathways. Created with Biorender.com

While it remains inconclusive if the outcomes reported in studies of COVID-19 ARDS patients differ from that of non-COVID-19 ARDS patients, there have been reports of an increased frequency of white matter abnormalities in COVID-19 ARDS patients relative to ARDS of other causes. A study by Kandemirli et al. (2020) found that COVID-19 patients with more severe respiratory symptoms had more severe white matter abnormalities on MRI. In addition, Pan et al. (2020) found that nonspecific white matter abnormalities were the most prevalent neuroradiological finding in a population of 628 COVID-19 ARDS patients. They are commonly observed in the brains of older adults, with prevalence increasing with age and vascular risk factors such as hypertension, diabetes, and smoking (Debette & Markus, 2010). Several risk factors have been identified that contribute to the development and progression of white matter hyperintensities (WMH). In addition to age and vascular risk factors, other factors such as genetics, lifestyle factors, and comorbid conditions may also play a role. WMH have been associated with cognitive decline, gait disturbance, depression, and an increased risk of stroke and dementia (Debette & Markus, 2010; Wardlaw et al., 2015). On MR fluid attenuated inversion recovery (FLAIR) imaging, WMH

appear as rounded, bright foci and decreased signal on T1-weighted MR imaging (Wardlaw et al., 2013).

WMH are thought to be manifestations of cerebral small vessel disease (CSVD) and are associated with disruption of the BBB (Wardlaw et al., 2015). CSVD is a group of pathological processes that affect the small vessels in the brain, including arterioles, capillaries, and venules. These pathological changes can lead to hypoperfusion, ischemia, and microvascular injury, thought to contribute to the development of WMH (Wardlaw et al., 2015). WMH are thought to result from chronic ischemia due to vascular damage, as evidenced by the increased presence of leaked proteins found in the perivascular space, and are associated with white matter axonal demyelination and gliosis (Wardlaw et al., 2013; Wardlaw et al., 2015).

1.12 Imaging Techniques in COVID-19 ARDS

Imaging techniques such as MRI, computed tomography (CT), and positron emission tomography (PET) have been utilized to investigate the neurological manifestations of COVID-19 ARDS. These imaging techniques provide useful information on brain morphology, structural changes, and metabolic activity in patients with COVID-19 ARDS. However, the dynamic nature of the data, along with the variability across scanners, highlight the need for robust methods of image analysis.

The Subspecialty Committee on Diagnostic Neuroradiology of the European Society of Neuroradiology (ESNR) established a dedicated NeuroCovid working group in 2022 aimed to address the standardization of imaging techniques for COVID-19 based on common manifestations. The use of CT in investigating COVID-19-related brain injuries may limit comprehensive documentation of brain injury in COVID-19 due to the potential for underestimation of small vessel infarct prevalence compared to the use of MRI with DWI (Blair et al, 2017). Cerebral microbleeds (CMBs) are frequently seen in MRI studies of COVID-19 ARDS patients, particularly those with higher inflammatory marker levels, and disturbances of consciousness and confusion. CMBs are readily observed using susceptibility weighted imaged (SWI). The exact cause of CMBs remains poorly understood, but several potential explanations have been proposed, including true microbleeds or intravascular microthrombi. These lesions are thought to result from a combination of pathophysiological mechanisms such as hypoxia,

ischemia, inflammation, thrombosis, and endothelial injury. The presence of these microbleeds is associated with increased mortality and worse functional outcomes in COVID-19 patients, suggesting their increased frequency may relate to severity of illness (Agarwal et al., 2020; Blair et al, 2017). SWI is a recommended sequence for use in critically ill COVID-19 patients and may be related to neurological symptoms. Leptomeningeal contrast enhancement, characterized by the enhancement of the meninges, has been observed in patients with severe COVID-19 and neurological symptoms and is best detected using contrast-enhanced 3D FLAIR imaging in COVID-19 patients (Velonakis et al., 2021). The three-dimensional (3D) magnetization-prepared rapid gradient echo (MP-RAGE) sequence is also commonly utilized for obtaining high-resolution whole brain T1-weighted images and provides improved tissue contrast with full brain coverage. MP-RAGE sequences are commonly used in critically ill patient groups due to improved brain tissue classification and estimation of regional brain volume (Nelson et al., 2008).

Recent studies have proposed various methods of brain image analysis in COVID-19 ARDS, including manual segmentation, region-of-interest (ROI) analysis, machine learning algorithms, and deep learning models. These methods have been shown to be effective in detecting subtle changes in brain structure and function that may not be apparent on visual inspection alone. Machine learning algorithms have been used to predict neurological outcomes in COVID-19 patients (Zhang et al, 2023). Deep learning models have been employed to detect white matter abnormalities and cerebral microbleeds in COVID-19 patients (Napolitano et al, 2022). The use of these advanced image analysis methods has enabled researchers to identify novel imaging findings in COVID-19 ARDS patients.

1.13 Objectives

The objective of this thesis is to identify patterns and locations of brain injuries presented in COVID-19 ARDS patient groups and explore MRI approaches for quantification of disease-specific brain injuries. First, in Chapter 2 of this thesis, we conducted a systematic review of brain imaging findings in COVID-19 ARDS and compared pooled results from several studies to findings in non-COVID-19 ARDS patient groups. WMH were commonly reported in COVD-19 ARDS patients, an important but underexplored finding, which we aim to explore further using MRI. In chapter 3 of this thesis, we proposed an MR image analysis pipeline for quantification of WMH, combining preprocessing de-noising steps and a novel automated WMH segmentation

technique created specifically to enable improved and standardized group level analyses for assessing WMH in a multicenter dataset of patients with COVID-19 ARDS. The impact of differing preprocessing methods on WMH quantification is described. An optimal image preprocessing method that improves on automated segmentation of WMH was explored to enable further studies on associations of WMH in ARDS patients with established quantification metrics such as Fazekas score.

The overarching goal of this work is to understand the brain injuries important in COVID-19 ARDS and their potential mechanisms. In chapter 4, a summary of the main findings of this thesis is presented with implications for future work in understanding diagnostic and therapeutic targets for neurological outcomes in ARDS patient groups.

1.14 References

1. Abdelrahman Z, Li, M., Wang X. (2020). Comparative Review of SARS-CoV-2, SARS-CoV, MERS-CoV, and Influenza A Respiratory Viruses. *Frontiers in Immunology*, 11.
2. Ackermann, M., Verleden, S.E., Kuehnel, M., Haverich, A., Welte, T., Laenger, F., Vanstapel, A., Werlein, C., Stark, H., Tzankov, A., Li, W.W., Li, V.W., Mentzer, S.J., Jonigk, D. (2020). Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. *N Engl J Med*, 9;383(2), 120-128.
3. Agarwal, S., Jain, R., Dogra, S., Krieger, P., Lewis, A., Nguyen, V., Melmed, K., Galetta, S. (2020). Cerebral Microbleeds and Leukoencephalopathy in Critically Ill Patients With COVID-19. *Stroke*, 51(9), 2649-2655.
4. Arabi, Y. M., Harthi, A., Hussein, J., Bouchama, A., Johani, S., Hajeer, A. H., & Saeed, B. T. (2015). Severe neurologic syndrome associated with Middle East respiratory syndrome corona virus (MERS-CoV). *Infection,* 43(4), 495-501
5. The ARDS Definition Task Force*. (2012). Acute Respiratory Distress Syndrome: The Berlin Definition. *JAMA,* 307(23), 2526–2533.
6. Bakhtazad, A., Garmabi, B., Joghataei, M.T. (2021). Neurological manifestations of coronavirus infections, before and after COVID-19: a review of animal studies. *J Neurovirol,* 27(6), 864-884
7. Bain, W., Yang, H., Shah, F., Suber, T., Drohan, C, Yousif, N., DeSensi, R., Bensen N., Shaefer, C., Rosborough, B, Somasundaram, A. (2021). COVID-19 versus Non–COVID-19 Acute Respiratory Distress Syndrome: Comparison of Demographics, Physiologic Parameters, Inflammatory Biomarkers, and Clinical Outcomes. *Annals Amer Thorac Soc*, 18(7).
8. Batlle, D., Soler, M. J., Sparks, M. A., Hiremath, S., South, A. M., & Welling, P. A. (2020). Acute kidney injury in COVID-19: Emerging evidence of a distinct pathophysiology. *J Amer Soc Nephrol*, 31(7), 1380-1383.
9. Blair, G.W., Hernandez, M.V., Thrippleton, M.J., Doubal, F.N., Wardlaw, J.M. (2017). Advanced Neuroimaging of Cerebral Small Vessel Disease. *Curr Treat Options Cardio Med,* 19, 56.

10. Beigel, J. H., Tomashek, K. M., Dodd, L. E., Mehta, A. K., Zingman, B. S., Kalil, A. C., & Lopez de Castilla, D. (2020). Remdesivir for the treatment of Covid-19—Final report. *New Eng J Med*, 383(19), 1813-1826.
11. Bellani, G., Laffey, J. G., Pham, T., Fan, E., Brochard, L., Esteban, A., & Pesenti, A. (2016). Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. *JAMA*, 315(8), 788-800.
12. Calfee CS, Eisner MD, Ware LB, Thompson BT, Parsons PE, Wheeler AP, Korpak A, Matthay MA. (2007). Acute Respiratory Distress Syndrome Network, National Heart, Lung, and Blood Institute. Trauma-associated lung injury differs clinically and biologically from acute lung injury due to other clinical disorders. *Crit Care Med,* 35(10):2243-50.
13. Centers for Disease Control and Prevention. (2021). COVID-19: Symptoms of COVID-19. Retrieved from https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html
14. Chacón-Aponte AA, Durán-Vargas ÉA, Arévalo-Carrillo JA, Lozada-Martínez ID, Bolaño-Romero MP, Moscote-Salazar LR, Grille P, Janjua T. (2022). Brain-lung interaction: a vicious cycle in traumatic brain injury. *Acute Crit Care,* 37(1), 35-44.
15. Chen, G., Wu, D., Guo, W., Cao, Y., Huang, D., Wang, H., & Zhang, X. (2020). Clinical and immunological features of severe and moderate coronavirus disease 2019. *J Clin Investigation*, 130(5), 2620-2629.
16. Clerkin, K. J., Fried, J. A., Raikhelkar, J., Sayer, G., Griffin, J. M., Masoumi, A., Sneha, S., Burkhoff, D., Kumaraih, D., Rabbani, L., Schwartz, A., Uriel, N. (2020). COVID-19 and cardiovascular disease. *Circulation,* 141(20), 1648-1655.
17. Combes, A., Hajage, D., Capellier, G., Demoule, A., Lavoué, S., Guervilly, C., Da Silva, D., Zafrani, L., Tirot, P., Veber, B., Maury, E., Levy, B. (2018). Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. *New Eng J Med,* 378, 1965-1975.
18. Connors, J. M., & Levy, J. H. (2020). COVID-19 and its implications for thrombosis and anticoagulation. *Blood*, 135(23), 2033-2040.

19. Contant, C.F., Valadka, A.B., Shankar, P., Gopinath, M.D., Hannay, J., Robertsion, C.S. (2001). Adult respiratory distress syndrome: a complication of induced hypertension after severe head injury. *J Neurosurg,* 95, 560–568.
20. Davidson AM, Wysocki J, Batlle D. (2020). Interaction of SARS-CoV-2 and Other Coronavirus With ACE (Angiotensin-Converting Enzyme)-2 as Their Main Receptor: Therapeutic Implications. *Hypertension,* 76(5), 1339-1349.
21. Debette, S., & Markus, H. S. (2010). The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: Systematic review and meta-analysis. *British M J*, 341, c3666.
22. Douaud, G., Lee, S., Alfaro-Almagro, F. (2022). SARS-CoV-2 is associated with changes in brain structure in UK Biobank. *Nature* 604, 697–707.
23. El-Solh A, Meduri U, Lawson Y, Carter M, Mergenhagen K. (2021). Clinical Course and Outcome of COVID-19 Acute Respiratory Distress Syndrome: Data From a National Repository. *J Intensive Care Med*, 36(6), 664–672.
24. European Society of Neuroradiology (ESNR). NeuroCovid: Imaging in COVID-19 Working Group. Retrieved from https://www.esnr.org/neurocovid-imaging-in-covid-19-working-group
25. Fan, E., Del Sorbo, L., Goligher, E. C., Hodgson, C. L., Munshi, L., Walkey, A. J., Adhikari, N.K.J., Amato, M.B.P., Branson, R., Brower, R.G., Ferguson, N.D., Gajic, O., Gattinoni, L., Hess, D., Mancebo, J., Meade, M., Mcauley, D.F., Pesenti, A., Raneiri, M., Rubenfield, G., Rubin, E., Seckel, M., Slutsky, A., Talmor, D., Thompson, T., Wunsch, H., Uleryk, E., Brozek, J., Brochard, L. (2017). An Official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine Clinical Practice Guideline: Mechanical Ventilation in Adult Patients with Acute Respiratory Distress Syndrome. *Amer J Respir Crit Care Med,* 195(9), 1253-1263.
26. Gibson PG, Qin L, Puah SH. (2020). COVID-19 acute respiratory distress syndrome (ARDS): clinical features and differences from typical pre-COVID-19 ARDS. *Med J,* 213(2), 54-56.
27. Girard T.D., Jackson JC, Pandharipande PP, Pun BT, Thompson JL, Shintani AK, Gordon SM, Canonico AE, Dittus RS, Bernard GR, Ely EW. (2010). Delirium as a

predictor of long-term cognitive impairment in survivors of critical illness. *Crit Care Med*, 38(7).

28. Gottlieb, R. L., Nirula, A., Chen, P., Boscia, J., Heller, B., Morris, J., & Cardona, J. (2021). Effect of bamlanivimab as monotherapy or in combination with etesevimab on viral load in patients with mild to moderate Covid-19: A randomized clinical trial. *JAMA*, 325(7), 632-644.
29. Grommes, J., & Soehnlein, O. (2011). Contribution of neutrophils to acute lung injury. *Mol Med*, 17(3-4), 293-307
30. Hernández-Parra H, Reyes-Hernández OD, Figueroa-González G, González-Del Carmen M, González-Torres M, Peña-Corona SI, Florán B, Cortés H and Leyva-Gómez G. (2023) Alteration of the blood-brain barrier by COVID-19 and its implication in the permeation of drugs into the brain. *Front Cell Neurosci,* 17, 1125109.
31. Hong S, Hongye W, Zhaolong Z, Lujun, Q. (2022). The roles of methylprednisolone treatment in patients with COVID-19: A systematic review and meta-analysis. *Steroids,* 183, 109022.
32. Hopkins, R., Suchyta, M.R., Beene, K,. Jackson, J.C. (2016). Critical Illness Acquired Brain Injury: Neuroimaging and Implications for Rehabilitation. *Rehab Psychol*, 61(2), 151-164.
33. Hopkins, R.O., Weaver, L.K., Collingridge, D., Parkinson, R.B., Chan, K.J., Orme, J. (2005). Two-Year Cognitive, Emotional, and Quality-of-Life Outcomes in Acute Respiratory Distress Syndrome. *Amer J Respir Crit Care*, 171(4).
34. Huang, M., Gedansky, A., Hassett, C.E., Price, C., Fan, T.H., Stephens, R.S., Nyquist, P., Uchino, K., Cho, S.M. (2021). Pathophysiology of Brain Injury and Neurological Outcome in Acute Respiratory Distress Syndrome: A Scoping Review of Preclinical to Clinical Studies. *Neurocrit Care*, 35(2):518-527.
35. Huppert, L. A., Matthay, M. A., & Ware, L. B. (2019). Pathogenesis of acute respiratory distress syndrome. *Seminars Respir Crit Care Med*, 40(1), 31-39.
36. Jackson, J. C. , Hopkins, R. O. , Miller, R. R. , Gordon, S. M. , Wheeler, A.P., Ely, E. W. (2009). Acute Respiratory Distress Syndrome, Sepsis, and Cognitive Decline: A Review and Case Study. *Southern Med J*, 102 (11), 1150-1157

37. Jackson, J. C., Pandharipande, P. P., Girard, T. D., Brummel, N. E., Thompson, J. L., Hughes, C. G., Pun, B., Vasilevskis, E., Morandi, A., Shintani, A., Hopkins R.O., Dittus, G., R., Ely, E.W. (2014). Depression, post-traumatic stress disorder, and functional disability in survivors of critical illness in the BRAIN-ICU study: a longitudinal cohort study. *Lancet Respir Med*, 2(5), 369-379.
38. Kandemirli, S. G., et al. (2020). Brain MRI findings in patients in the intensive care unit with COVID-19 infection. *Radiology*, 297, E232-E235.
39. Karanikas E. (2021). Psychologically Traumatic Oxidative Stress; A Comprehensive Review of Redox Mechanisms and Related Inflammatory Implications. *Psychopharmacol Bull*, 51(4):65-86.
40. Matthay, M. A., Zemans, R. L., Zimmerman, G. A., Arabi, Y. M., Beitler, J. R., Mercat, A., Herridge, M., Randolph, A.G., Calfee, C.S. (2019). Acute respiratory distress syndrome. *Nat Rev Dis Prim,* 5, 18.
41. Marshall, R., Bellingan, G., Laurant, G. (1998). The acute respiratory distress syndrome: fibrosis in the fast lane. *Thorax,* 53:815-817
42. Mart, M.F., Ware, L.B. (2020) The long-lasting effects of the acute respiratory distress syndrome. *Expert Rev Respir Med*, 14(6), 577-586.
43. Mao, L., Jin, H., Wang, M., Hu, Y., Chen, S., He, Q., & Hu, B. (2020). Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol*, 77(6), 683-690.
44. Middleton E.A., Zimmerman G.A. (2021). COVID-19-Associated Acute Respiratory Distress Syndrome: Lessons from Tissues and Cells. *Crit Care Clin*, 37(4), 777-793.
45. Morandi, A,, Rogers, B.P., Gunther, M.L., Merkle, K., Pandharipande, P., Girard, T.D., Jackson, J.C., Thompson, J., Shintani, E.K., Geevarghese, S., Miller, R.R., Canonico, A., Cannistraci, C.J., Gore, J.C., Ely, E.W., Hopkins, R.O. (2012). The relationship between delirium duration, white matter integrity, and cognitive impairment in intensive care unit survivors as determined by diffusion tensor imaging: the VISIONS prospective cohort magnetic resonance imaging study*. *Crit Care Med*, 40(7), 2182-2189.
46. Napolitano, A., Arrigoni, A., Caroli, A., Cava, M., Remuzzi, A., Longhi, L.G., Barletta, A., Zangari, R., Lorini, F.L., Sessa, M., Gerevini, S. (2022) Cerebral Microbleeds

Assessment and Quantification in COVID-19 Patients With Neurological Manifestations. *Front Neurol*, 13, 88444

47. Nelson F, Poonawalla A, Hou P, Wolinsky JS, Narayana PA. (2008). 3D MPRAGE improves classification of cortical lesions in multiple sclerosis. *Mult Scler*, 14(9).
48. Ni, W., Yang, X., Yang, D. (2020). Role of angiotensin-converting enzyme 2 (ACE2) in COVID-19. *Crit Care,* 24, 422.
49. Otifi, H.M., Adiga, B.K. (2022). Endothelial Dysfunction in Covid-19 Infection. *Am J Med Sci,* 363(4), 281-287.
50. Petersen, M. E., Nagelle, F., Mayer, M., Schell M., Petersen, E., Kuhn, S., Gallinat, J., Fieler, J., Pasternak, O, Matcyek, J., Glatzel, M., Twerenbold, R., Gerloff, C., Thomalla, G., Cheng, B. (2023). Brain imaging and neuropsychological assessment of individuals recovered from a mild to moderate SARS-CoV-2 infection. *PNAS,* 120(22), e2217232120.
51. Pan, S., Chen, W., Baal, J., Sugrue, L. (2020). Neuroradiological Features of Mild and Severe SARS-CoV-2 Infection. *Academic Radiology*, 27(11), 1507-1514
52. Pandharipande, P. P., Girard, T. D., Jackson, J. C., Morandi, A., Thompson, J. L., Pun, B. T., Brummel, C.G., Hughes, E.E., Shintai, K.G., Moons, S.K., Geevarghese, A.C., Canonico, A., Hopkins, R.O., Bernard, G.R., Dittus, R.S., Ely, E.W. (2013). Long-term cognitive impairment after critical illness. *New Eng J Med,* 369, 1306-1316.
53. Pun, B. T., Badenes, R., Heras La Calle, G., Orun, O. M., Chen, W., Raman, R., & Navarro, B. F. (2021). Prevalence and risk factors for delirium in critically ill patients with COVID-19 (COVID-D): a multicentre cohort study. *Lancet Respir Med*, 9(3), 239-250.
54. Reiss, L. K., Uhlig, U., Uhlig, S. (2012). Models and mechanisms of acute lung injury caused by direct insults. *Europ J Cell Bio*, 91(6-7), 560-601.
55. Saad, M., Omrani, A. S., Baig, K., Bahloul, A., Elzein, F., Matin, M. A., & Memish, Z. A. (2014). Clinical aspects and outcomes of 70 patients with Middle East respiratory syndrome coronavirus infection: a single-center experience in Saudi Arabia. *International J Infect Dis,* 29, 301-306.

56. Salama, C., Han, J., Yau, L., Reiss, W. G., Kramer, B., Neidhart, J. D., & Zhang, J. (2021). Tocilizumab in patients hospitalized with Covid-19 pneumonia. *New Eng J Med,* 384(1), 20-30.
57. Sanders, J. M., Monogue, M. L., Jodlowski, T. Z., Cutrell, J. B. (2020). Pharmacologic treatments for coronavirus disease 2019 (COVID-19): A review. *JAMA,* 323(18), 1824-1836.
58. Sasannejad C, Ely EW, Lahiri S. (2019). Long-term cognitive impairment after acute respiratory distress syndrome: a review of clinical impact and pathophysiological mechanisms. *Crit Care,* 23(1), 352.
59. Semeraro N, Colucci M. (2021). The Prothrombotic State Associated with SARS-CoV-2 Infection: Pathophysiological Aspects. *Mediterr J Hematol Infect Dis,* 1;13(1), e2021045.
60. Shahjouei, S., Naderi, S., Li, J., Khan, A., Chaudhary, D., Farahmand, G., & Zand, R. (2020). Risk of stroke in hospitalized SARS-CoV-2 infected patients: A multinational study. *EbioMedicine*, 59, 102939.
61. Shankar-Hari, M., Fan, E., Ferguson, N. D., & Rubenfeld, G. D. (2019). Acute respiratory distress syndrome (ARDS) phenotyping. *Intens Care Med*, 45, 516-519.
62. Sharma S. (2010). Acute respiratory distress syndrome. *BMJ Clin Evid*, 30, 1511.
63. Shaver, C.M., Bastarache, J.A. (2014). Clinical and biological heterogeneity in acute respiratory distress syndrome: direct versus indirect lung injury. *Clin Chest Med,* 35(4):639-653.
64. Shoskes, A., Huang, M., Gedansky, A., Hassett, C., Buletko, A.B., Duggal, A., Uchino, K., Cho, S., (2022). MRI of Cerebrovascular Injury Associated With COVID-19 and Non-COVID-19 Acute Respiratory Distress Syndrome: A Matched Case-Control Study. *Crit Care Med*, 50(11), 1638-1643
65. Siddiqi, H. K., Mehra, M. R. (2020). COVID-19 illness in native and immunosuppressed states: A clinical-therapeutic staging proposal. *J Heart Lung Transplant*, 39, 405-407.
66. Sonneville, R., Verdonk, F., Rauturier, C., Klein, I. F., Wolff, M., Annane, D., Chretien, F., Sharshar, T. (2013). Understanding brain dysfunction in sepsis. *Ann Intens Care*, 3(1), 15.
67. Sterne, J. A., Murthy, S., Diaz, J. V., Slutsky, A. S., Villar, J., Angus, D. C., & Perner, A. (2020). Association between administration of systemic corticosteroids and mortality

among critically ill patients with COVID-19: A meta-analysis. *JAMA,* 324(13), 1330-1341.

68. Taquet, M., Geddes, J. R., Husain, M., Luciano, S., & Harrison, P. J. (2021). 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. *Lancet Psych*, 8(5), 416-427.
69. Tian, Y., Rong, L., Nian, W., Yan, H. (2020). Review article: Gastrointestinal features in COVID-19 and the possibility of faecal transmission. *Alimen Pharm & Therap,* 51(9), 843-851.
70. Umapathi, T., Kor, A.C., Venketasubramanian, N., Tchoyoson, C.C., Pang, B.C., Yeo, T.T., Lee, C.C., Lim, P.L., Ponnudurai, K., Chuah, K.L., Tan, P.H., Tai, D.Y.H., Ang, S.P.B. (2004). Large artery ischaemic stroke in severe acute respiratory syndrome (SARS*). J Neurol* 251, 1227–1231.
71. Velonakis G, Karavasilis E, Filippiadis DK, Almyroudi MP, Korompoki E. (2021). Leptomeningeal Enhancement Due to COVID-19 on 3D-FLAIR and T1 Black-Blood MR Imaging Sequences. *AJNR Am J Neuroradiol*, 42(7), E39-E41.
72. Wang, Z., Yang, Y., Liang, X., Gao, B., Liu, M., Li, W., Chen, Z., Wang, Z. (2020). COVID-19 associated ischemic stroke and hemorrhagic stroke: Incidence, potential pathological mechanism, and management. *Front Neurol*, 11, 571996.
73. Wardlaw, J. M., et al. (2013). Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol*, 12, 822-838.
74. Wardlaw, J.M., Valdés-Hernández, M.C., Muñoz-Maniega, S. (2015). What are white matter hyperintensities made of? Relevance to vascular cognitive impairment. *J Am Heart Assoc,* 4(6), 001140.
75. Ware, L. B., & Matthay, M. A. (2000). The acute respiratory distress syndrome. *New Eng J Med,* 342(18), 1334-1349.
76. Wang, L., Davis, P.B., Volkow, N.D., Berger, N.A., Kaelber, D.C., Zu, Rong. (2022). Association of COVID-19 with New-Onset Alzheimer's disease. *J Alzheimer's Dis*, 89, 411-414.

77. Wild C.J., Norton, L., Menon, D.K., Ripsman, D.A., Swartz, R.H., Owen, A.M. (2023). Disentangling the cognitive, physical, and mental health sequelae of COVID-19. *Cell Rep Med,* 3(10):100750.
78. Williams, G.W., Berg, N.K., Reskallah, A., Yuan, X., Eltzschig, H.K. (2021). Acute Respiratory Distress Syndrome: Contemporary Management and Novel Approaches during COVID-19. *Anesthesiology,* 134(2), 270-282.
79. Wool, G.D., Miller, J.L. (2020). The Impact of COVID-19 Disease on Platelets and Coagulation. *Pathobiology,* 88(1), 15-27.
80. World Health Organization. (2021). WHO Coronavirus (COVID-19) Dashboard. Retrieved from https://covid19.who.int/
81. Wu, C., Chen, X., Cai, Y., Xia, J., Zhou, X., Xu, S., & Song, Y. (2020). Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Internal Med,* 180(7), 934-943.
82. Zhang, H., Zang, C., Xu, Z. (2023). Data-driven identification of post-acute SARS-CoV-2 infection subphenotypes. *Nat Med,* 29, 226–235.
83. Ziehr, D. R., Alladina, J., Petri, C. R., Maley, J. H., Moskowitz, A., Medoff, B. D., & Hibbert, K. A. (2020). Respiratory pathophysiology of mechanically ventilated patients with COVID-19: A cohort study. *Amer J Respir Crit Care Med,* 201(12), 1560-1564.

Chapter 2

2 Spectrum of brain injury in COVID-19-acute respiratory distress syndrome (ARDS): A systematic review and meta-analysis

A version of this chapter is undergoing submission to Lancet Neurology.

While the majority of COVID-19 patients present with mild respiratory symptoms, many of those hospitalized with severe infection progress to develop ARDS, typically requiring ICU admission and supplemental oxygenation or mechanical ventilation. Outcomes for these patients are poor, including increased duration of ventilation and ICU stay, cognitive and psychiatric impairment, and higher risk of mortality. The aim of this systematic review is to compare neuroimaging findings in patients with COVID-19 ARDS versus non-COVID-19 ARDS. The results of this systematic review indicate that COVID-19 ARDS patients are twice as likely to develop ICH than non-COVID-19 ARDS patients and present with a distinct pattern of brain injury particularly localized to white matter. Methodologic limitation of included original studies (i.e. small sample size, retrospective cohort and case-series designs, heterogenous patient populations) make it difficult to fully attribute observed differences to COVID-19 ARDS status and should be interpreted as hypothesis generating. . Changes in brain structure and function may indicate increased risk in some patients for the development of significant health issues in survivors, knowledge of which can be used to develop potential intervention targets for current and future patients.

2.1 Study Aims and Objectives

The Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) virus was first reported in late 2019 and has since spread rapidly around the world. While most patients present with mild respiratory illness, a recent cohort study reported that as many as 61-85% of ICU patients admitted due to severe coronavirus disease of 2019 (COVID-19) infection met the Berlin Criteria definition (ARDS Definition Task Force, 2021) of ARDS, the most frequent life-threatening complication of COVID-19 (Wu et al. 2021; Ziehr et al. 2020; El-Solh et al. 2021). COVID-19 ARDS patients are susceptible to neurologic complications. Brain injury can occur as a result of direct viral injury to the brain, or indirect injury due to systemic consequences of COVID infection such as

inflammation, or ARDS treatments inclusive of ventilation, anticoagulation and sedatives that these patients receive. Research examining neurological outcome and differences in COVID-19 ARDS and non-COVID-19 ARDS patients remains limited, largely due to small sample sizes and paucity of data (Bain et al., 2020; Brault et al., 2020).

Neuroimaging can shed light on the type, prevalence, and distribution of COVID-related brain injury, but this has not yet been summarized. While many studies have characterized the clinical presentation of ARDS and COVID-19 induced respiratory failure, there is limited evaluation of neuroimaging findings in these patients, which could provide valuable insights into the pathophysiology of neurocognitive impairment among ARDS survivors and long-COVID-19. Most studies have a limited number of participants, which may not be representative of the larger population of COVID-19 patients with ARDS. The pathophysiology underlying cerebrovascular insults is unclear but may relate to direct brain injury from the SARS-CoV-2 virus or from sequelae of associated hypoxia, ischemia, endothelial injury, or inflammation commonly seen in COVID-19 (Bain et al. 2021). In this systematic review and meta-analysis, we collated existing neuroimaging evidence regarding type, prevalence, and distribution of COVID-19 ARDS related brain injury and compared it to non-COVID-19 ARDS patients.

The objective of this review is to compare neuroimaging findings in patients with COVID-19 ARDS versus non-COVID-19 ARDS. This review will specifically focus on findings obtained using advanced neuroimaging techniques such as MRI, computed tomography (CT), or positron emission tomography (PET). By summarizing the neuroimaging outcomes in ARDS brain injury, we highlight similarities and differences between COVID-19 ARDS and non-COVID-19 ARDS, identify research gaps to inform future research, and inform clinical practice. A better understanding of the neuroimaging findings in COVID-19 ARDS can lead to improved treatment strategies, which can improve patient outcomes. COVID-19 ARDS also great clinical relevance for healthcare providers as summarized neuroimaging data can improve treatment planning, allow for better patient management, and better identification of future research needs.

2.2 Study Selection and Bias Assessment

This is a systematic review and meta-analysis of studies comparing the type, frequency and location of brain injury detected on neuroimaging in patients with COVID-19 ARDS and non-

COVID-19 ARDS. The protocol for this systematic review and meta-analysis was registered in the Prospective Register of Ongoing Systematic Reviews (PROSPERO) (registration number: CRD42021251620) and conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-analyses 2020 (Page et al. 2021) guidelines.

We included prospective and retrospective, observational, randomized and non-randomized trials and case-series that met the following criteria: (1) enrolled adult (≥18 years old) patients, (2) who were admitted to any intensive care unit including general medical-surgical, trauma and subspecialty ICUs (for example cardiovascular, burns and neuro-based units), (3) with the diagnosis of ARDS defined as a PaO2:FiO2 ≤ 300 mm Hg and requiring invasive or non-invasive mechanical ventilation or high flow supplemental oxygen, (4) and who had neuroimaging (MRI, CT or PET) performed within 1 year of having COVID-19 infection and ARDS, and (5) a polymerase chain reaction (PCR) test was used to confirm SARS-CoV-2 infection and COVID-19 diagnosis (positive or negative).

We excluded studies that enrolled (1) pediatric patients due to difficulty controlling for the impact of brain development on outcomes, (2) were published in languages other than English, and (3) case reports, commentaries, letters, editorials, newspaper articles, conference abstracts, reviews, and commentaries. Full text articles that did not clearly describe their diagnostic criteria for ARDS, fail to describe COVID-19 diagnosis confirmation, or did not include brain MRI/CT/PET, or were conducted in pediatric population were excluded. A full list of exclusion criteria and the number of studies is outlined in Figure 2.2.

A clinical librarian with training in search strategies for systematic reviews performed a comprehensive electronic search in MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.gov, and World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) databases from August 1969 to August 2022. The search strategy included Medical Subject Headings (MeSH) and other keywords combined using Boolean terms to search the MEDLINE via Ovid, EMBASE interfaces, while combinations of keywords were used to search the other databases. Gray literature was searched on Google Scholar, "Cited by" feature was used to identify related studies, while search was done in browsers incognito mode to find recent publications. The comprehensive search strategy for

each database is available in the Appendix A. The search terms “COVID-19”, “SARS-CoV-2”, “acute respiratory distress syndrome”, “ARDS”, “Neuroimaging”, “MRI”, “CT”, and “PET” were used (see Table 1 for full search strategy).

Table 2.1: Medline search strategy

Database	Ovid MEDLINE(R) ALL
1	Respiratory Distress Syndrome/ (23251)
2	(respirator$ adj2 distress$ adj2 syndrom$).tw,kf. (34345)
3	ARDS.tw,kf. (17542)
4	((acute$ or adult$ or severe$) adj3 (respirator$ adj3 distress$)).tw,kf. (28504)
5	(lung$ adj2 shock$).tw,kf. (626)
6	(((post traumatic$ or posttraumatic$) adj3 (respirator$ or lung$)) and failure$).tw,kf. (73)
7	((post traumatic$ or posttraumatic$) adj3 pulmonar$ adj3 insufficienc$).tw,kf. (69)
8	exp Respiratory Insufficiency/ (67029)
9	(respirat$ adj3 (distress$ or failure$ or insufficien$ or paralysis$ or deficienc$ or disturbanc$ or depression)).tw,kf. (106383)
10	(acute$ and ((respirat$ adj2 insufficienc$) or (respirat$ adj2 failure$))).tw,kf. (18981)
11	Acute Lung Injury/ (7776)
12	(acute$ and (lung$ adj2 injur$)).tw,kf. (20854)
13	((lung$ or pulmonary$) adj3 (failure$ or insufficien$)).tw,kf. (11010)
14	or/1-13 [Seach Concept: adult respiratory distress syndrome MEDLINE] (182927)
15	Critical Care/ or Critical Illness/ or (critical$ or intensive*).jw,ja,jn. or critically$.tw,kf. or (critical$ adj2 ill$).mp. (334058)
16	exp intensive care units/ or (ICU or ICUs or ((intensive care$ or intensive therapy$ or intensive treatment$ or high dependency$ or (coronary$ adj2 care$) or critical$ care) adj2 unit$) or MICU or CICU or CVICU or CCU$1 or SICU or POCCU$1 or HDU?ITU or ITU$1 or HDU$1).mp. or (critical$ and (intensive adj care)).mp. or (intensiv$ therap$ or intensiv$ treat$).tw,kf. (236567)
17	exp Respiration, Artificial/ or exp Ventilators, Mechanical/ or (ventilat$ adj2 (artificial$ or mechanical$)).tw,kf. or (respirat$ adj2 (artificial$ or assisted$ or mechanical$)).tw,kf. or (respirat$ adj2 failure$).tw,kf. (159024)

18	(ventilat$ adj2 (weaning or support$)).tw,kf. or ((positive adj3 pressure adj5 (ventilat$ or respir$)) or (PPV and (pressure or ventilat$))).tw. or (ventilat$ adj3 patient$).ti. or (ventilat$ and patient$).ab. /freq=3 (49319)
19	19 or/15-18 (604907)
20	20 14 and 19 (77965)
21	21 exp diagnostic techniques, neurological/ (428999)
22	22 exp Brain/dg or Brain Diseases/dg [Diagnostic Imaging] (98899)
23	23 (neuronavigat$ or neuro-navigat$ or neuroimag$ or neuro-imag$ or (neurolog$ adj3 (evaluat$ or assess$ or examin$)) or neuroradiogr$ or neuro-radiogr$).tw,kf.
24	24 (thickness$ adj3 (cortical$ or brain or cerebral$ or cortex$)).tw,kf.
25	25 Positron-Emission Tomography/ or "Fluorodeoxyglucose F 18"/ or (f-18$ or f18$ or fluorine-18$ or 18f$ or 18-f$ or fluorodeoxyglucose$ or FDG$).tw,kf.
26	26 ((PET$ or "P.E.T.") and (scan$ or imag$3 pr stag$ or F-18$ or f18$ or 18f$ or 18-f$ or fluorine-18$ or fluorodeoxyglucose$ or FDG$)).tw,kf.
27	27 exp Magnetic Resonance Imaging/ (513892)
28	28 (magnetic resonance imag$ or imaging$ or mri$ or fMRI$ or (fluid?attenuat$ inversion$ recover$ or FLAIR)).tw,kf.
29	29 exp Tomography, X-Ray Computed/ (478476)
30	30 ((cat or ct$) adj2 (scan$ or x?ray or examination or imag$ or compute$ or diagnos$)).tw,kf.
31	31 PET?CT.tw,kf.
32	32 or/21-31 [imaging filter_MEDLINE]
33	33 (cerebr$ or intra?cerebral$ or cortical$ or subcortical$ or sub-cortical$ or cortex or brain$ or neurolog$).mp. or exp Brain Diseases/ or (brain$ adj5 (disease$ or disorder$)).tw,kf.
34	34 (hyperintens* or ((white$ or white?gr?y$) adj3 matter$) or lepto?mening$ or meningitis$ or meningo?encephalitis or demyelination or dysmyelination or myelitis or leukoencephalopath$ or encephal* or ADEM).tw,kf.
35	or/33-34 (3183788)
36	32 and 35 (779305)
37	20 and 36 [Q 1 set_Non-COVID-ARDS cohorts _Neuroimaging_Brain Injury] (1658)

38	((((exp Coronavirus/ or exp Coronavirus Infections/ or (D614G or coronavirus* or corona virus* or OC43 or NL63 or 229E or HKU1 or HCoV* or ncov* or covid* or sars-cov* or sarscov* or Sars-coronavirus* or Severe Acute Respiratory Syndrome Coronavirus*).mp.) and ((20191* or 202*).dp. or 20190101:20301231.(ep).)) not (SARS or SARS-CoV or MERS or MERS-CoV or Middle East respiratory syndrome or camel* or dromedar* or equine or coronary or coronal or covidence* or covidien or influenza virus or HIV or bovine or calves or TGEV or feline or porcine or BCoV or PED or PEDV or PDCoV or FIPV or FCoV or SADS-CoV or canine or CCov or zoonotic or avian influenza or H1N1 or H5N1 or H5N6 or IBV or murine corona*).mp.) or ((((pneumonia or covid* or coronavirus* or corona virus* or ncov* or 2019-ncov or sars*).mp. or exp pneumonia/) and Wuhan.mp.) or (2019-ncov or ncov19 or ncov-19 or 2019-novel CoV or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or coronavirus-19 or covid19 or covid-19 or covid 2019 or ((novel or new or nouveau) adj2 (CoV on nCoV or covid or coronavirus* or corona virus or Pandemi*2)) or ((covid or covid19 or covid-19) and pandemic*2) or (coronavirus* and pneumonia)).mp. or COVID-19.rx,px,ox. or severe acute respiratory syndrome coronavirus 2.os.)) and 20191201:20301231.(dt). (273094)
39	14 and 36 and 38 [Q2 set_COVID-19 ARDS cohorts _Neuroimaging_Brain Injury] (202)
40	37 or 39 (1723)
41	limit 40 to english language (1488)
42	41 not (exp Animals/ not (Human/ and exp Animals/)) (1446)
43	(mice or rat or rats or cat$1 or cattle$1 or dog$1 or goat$1 or horse$1 or rabbit$1 or sheep$1 or swine$1 or pig$1 or canine$1 or feline$1 or porcine$ or calf).ti. (1852344)
44	42 not 43 (1444)
45	(pediatr$ or paediatr$ or child$ or adolescent$ or infan$ or newborn$ or neonat$).ti. (1508333)
46	44 not 45 (1190)
47	limit 46 to "all adult (19 plus years)" (704)
48	limit 46 to "all child (0 to 18 years)" (234)
49	46 not (48 not (47 and 48)) (1032)
50	exp case-control studies/ or (case$ and control$).tw. or (case$ and series).tw. [Medline case series] (1884486)
51	case reports/ or case report$.mp. (2369310)
52	49 not (51 not (50 and 51)) (489)
53	52 not case report.ti. [Removing case Reports and retaining Case Series] (477)

The search results were uploaded to Covidence software that automatically screened and removed duplicate studies. Two reviewers (R.W. and J.C.) independently screened titles and abstracts and applied inclusion/exclusion criteria to identify articles for full text review. The same reviewers then screened full text titles to identify articles for data extraction. Disagreements between reviewers were resolved by discussion, consensus, and, when necessary, adjudication by a third reviewer (M.S.).

Two reviewers (R.W. and J.C.) independently and in duplicate extracted group summary statistics from all studies utilizing a predesigned Excel data extraction database. The following variables were extracted: first author name, date of publication, study design, location of publication, sample size, imaging modality, days from hospital admission to neuroimaging, source of funding, types of brain injury, frequency of brain injuries, locations of brain injury, age, sex, comorbidities, severity of illness scores, ventilatory parameters, sedation depth and agents, baseline laboratory results, and treatments.

Primary outcome was frequency of reported brain injury stratified by type and COVID-19 status. Secondary outcome was location of brain injury stratified by COVID-19 status.

2.3 Statistical Analyses

We used descriptive statistics to summarize frequency (mean ± SD for normally distributed, or median/IQR for non-normally distributed variables) of extracted variables across studies. We used a meta-analysis of single proportions of ICH frequency in COVID-19 ARDS and non-COVID-19 ARDS patients using a random-effects model because of heterogeneity across studies. We used risk ratio [95% CI] to report risk of ICH in COVID-19 ARDS patients versus non-COVID-19 ARDS patients. All meta-analyses were performed using the general linear mixed model method. All analyses were conducted in R with the package ‘meta’ using the metaprop function (R Core Team, 2021). A post-hoc sensitivity analysis was conducted for all meta-analyses to assess for studies contributing greatly to heterogeneity (calculated by I^2) for removal. Between study variance ($\tau 2$) was estimated using the maximum likelihood method. All meta-analyses conducted with available data were included in Appendix C. In addition, a Chi-Squared test was used to assess for preference of neuroimaging modality within each group.

We used 3-dimensional brain maps to report location of brain injury stratified by brain injury type and COVID-19 diagnosis. We created a graphical representation of brain injury using the Automatic Anatomical Labelling (AAL) brain atlas. To do this, we calculated weighted averages of frequencies of brain injuries across studies, pooled the findings, and stratified them by COVID-19 status and types of injuries (see Appendix B). Frequencies were then mapped onto corresponding brain regions in Matlab (version R2022a) using the AAL Atlas in SPM 12 in standard imaging space (Maldjian et al. 2003). The generated frequency map was normalized and processed using FreeSurfer's image analysis suite (version 7.3.2) and default parameters (recon-all-pipeline). The recon-all pipeline performs a joint registration-segmentation procedure that aligns the generated frequency to an internal FreeSurfer volumetric space (Fischl et al. 2002). FreeSurfer automatically reconstructs surface mesh representations from frequency and location data which is then inflated into a sphere and registered to a common spherical coordinate system (Fischl et al. 2002). The outcome of this procedure is nonlinear mapping between the native MNI space set to FreeSurfer's default fsaverage surface temaplate as a common space. The normalized frequency map was thus reconstructed to generate a cortical projection of the frequency map for visualization of the regional distribution of brain injury in COVID-19 ARDS and non-COVID-19 ARDS.

Since there were no randomized controlled trials, we used the adapted Newcastle-Ottawa Scale (NOS) to assess risk of bias in the included studies (see Figure 2.1 for comprehensive bias assessment. The overall quality of evidence was subsequently rated as "high", "unclear", or "low." Two reviewers (R.W. and J.C.) independently assessed risk of bias in all eligible studies and disagreements were resolved by discussion and consensus. The NOS scale assesses the following: 1. selection bias, which evaluates whether the participant group was adequately defined, the representative of the patient group, whether selection criteria were defined adequately, and how data was verified, 2. comparability, which evaluates how effectively the study addressed confounding factors in their analysis, and how clearly patient demographics were defined, and 3. outcome bias, which evaluates the rate of non-response and exclusion, whether measures were implemented consistently and reliably across the sample, whether outcomes were independently assessed and confirmed, and if outcomes were defined clearly and pre-specified (see Figure 2.1).

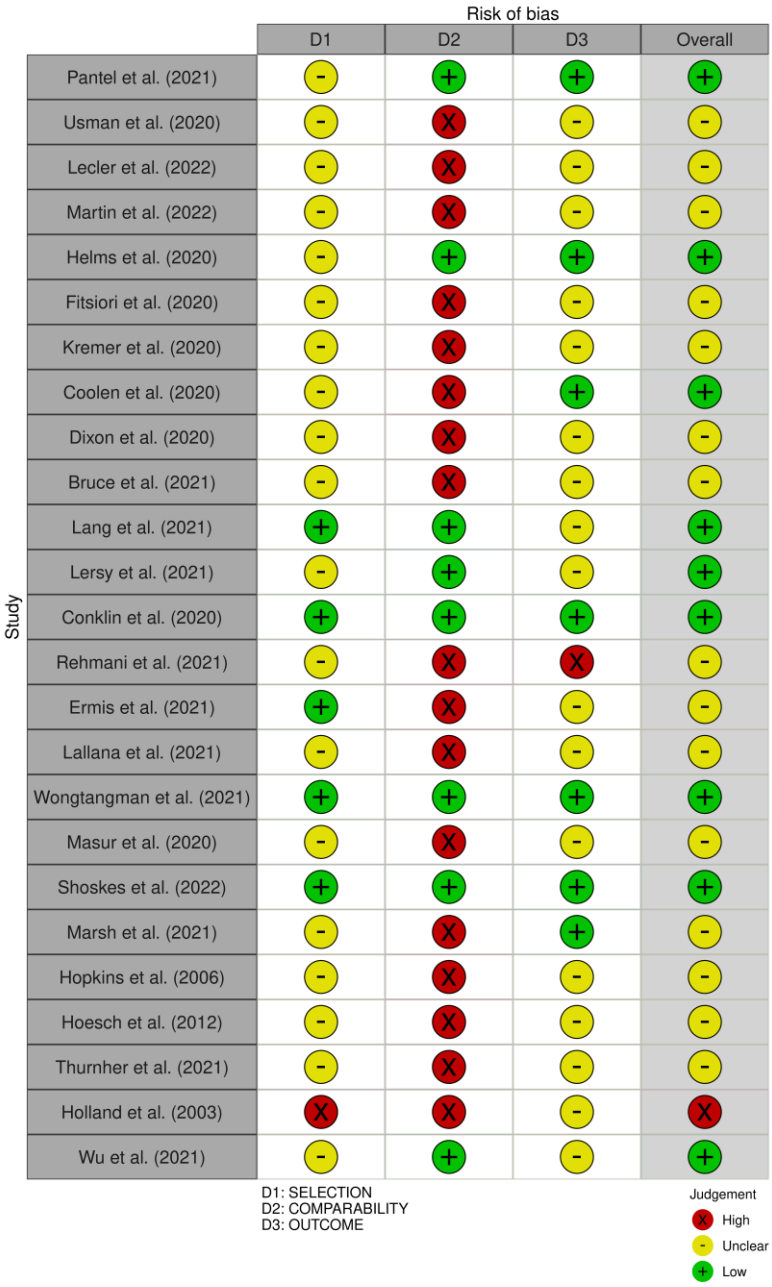


Figure 22.1: Risk of bias summary using the Newcastle-Ottawa Scale

2.4 Results

Our search strategy identified a total of 1,733 titles using database search, 131 studies identified through citation searching, 248 identified through website searching (see Figure 2.2). After removing 787 duplicates, 1,325 studies were screened using titles and abstracts. Of these, 1,090 were excluded, leaving 235 studies for full text screening. Full text screening excluded additional 206 studies, leaving 29 studies that enrolled a total of 1,067 patients (390 COVID-19 and 677 non-

COVID ARDS). For COVID-19 ARDS studies, ten were cohort (eight retrospective, two prospective) and nine were case series study design (five retrospective, four retrospective). For non-COVID-19 ARDS studies, one was case control (retrospective), eight were cohort (six retrospective, two prospective), and one was a case series (retrospective) study design. The largest study enrolled 156 non-COVID ARDS patients and the smallest study enrolled six COVID-19 ARDS patients. The majority of studies were from Europe and North America and used either CT or MRI to report neuroimaging findings (Table 2.2).

Table 2.2: Study characteristics

Author (year)	Study Design	Location	n°	Imaging modality	Day from admission to Neuroimaging Mean, *Median (range)*	Industry Funded (Yes/No); Disclosure
COVID-19 ARDS						
Pantel et al. (2021)	Cohort; Retrospective, Single Center, Academic Hospital	Germany	48	CT	9 (1-17)	No
Usman et al. (2020)	Case Series; Retrospective, Single Center, Academic Hospital	US	10	CT	..	..
Lecler et al. (2022)	Case Series, Retrospective, Multicenter, General Hospital, Academic Hospital	France	9	MRI	..	*Yes;* Authors received grants/payments from Roche and Bayer
Martin et al. (2022)	Case Series, Prospective, Single Center, Academic Hospital	Brazil	6	MRI, CT	..	Yes
Helms et al. (2020)	Cohort; Prospective,	France	28	MRI	28.8	Yes; Authors received

	Single Center, Academic Hospital					grants/payments from Johnson and Johnson, Actelion Pharmaceuticals, Teva, UCB, AbbVie, Aguettan, LVL, outside the submitted work
Fitsiori et al. (2020)	Case Series; Prospective, Single Center, Academic Center	Switzerland	9	MRI	..	..
Kremer et al. (2020)	Cohort; Retrospective; Multicenter, General Hospital, Academic Hospital	US	37	MRI	33 (21-46)	Yes; Association with AbbVie and Orkyn, AbbVie, Actelion Pharmaceuticals, Teva, LVL, Merz, and Aguettantt, Merz, LVL, Teva, Johnson & Johnson, Median Technologies, Edwards Lifesciences, Smiths Medical France, Pfizer, Sanofi, Gilead, Janssen, Astellas and Canon Medical Systems Europe
Coolen et al. (2020)	Case Series; Prospective, Single Center, General Hospital	Belgium	19	MRI	..	No
Dixon et al. (2020)	Case Series; Retrospective, Single Center, Academic Hospital	England	9	MRI	37.5 (24–59)	..

Bruce et al. (2021)	Case Series, Retrospective, Single Center, Academic Hospital	US	12	MRI, CT	18	No; Dr. Merkler has received personal fees for medico legal consulting on neurological disorders
Lang et al. (2021)	Cohort; Retrospective, Single Center, Academic Hospital	Germany	47	MRI, CT	20.4 ± 14.8 (2–47)	No
Lersy et al. (2021)	Cohort; Retrospective, Academic Hospital	France	19	MRI	19 (6-31)	..
Conklin et al. (2020)	Cohort; Retrospective, General Hospital	US	19	MRI	21.2 (13.7-30.9)	No; Authors have received research support from Siemens Healthineers, Zeus Scientific, bio-Merieux, GE Healthcare and Immunetics, and consulting fees from T2 Biosystems, Roche Diagnostics, GE Healthcare and Takeda Pharmaceutical and DiaSorin
Rehmani et al. (2021)	Cohort; Prospective, Single Center, General Hospital	Germany	16	MRI, CT	..	..
Ermis et al. (2021)	Cohort; Retrospective, Single Center, Academic Hospital	US	20	CT	..	..

Lallana et al. (2021)	Case Series, Prospective, Single Center, General Hospital	Spain	8	MRI, CT	31.3	..
Wongtangman et al. (2021)	Cohort; Retrospective, Single Center, General Hospital	Israel	36	MRI	..	No; Philanthropic donations from Jeffrey and Judy Buzen to Matthias Eikermann
Masur et al. (2020)	Case Series; Retrospective; Single Center; General Hospital	United States	12	MRI, CT	10.4	No; RSNA resident grant 2020-2021 to institution, NVIDIA GPU grant 2019, Consultancy: Northwest Biotherapeutics; Novocure, Galileo - Money paid to the institution
Shoskes et al. (2022)	Cohort; Retrospective; Single Center; Academic Hospital	United States	26	MRI	*30*	No; Funding from the National Heart, Lung, and Blood Institute and the Centers for Disease Control and Prevention; funding from On Steering committee for Alung Technologies.
ARDS						
Shoskes et al. 2022	Case Control; Retrospective; Single Center; Academic Hospital	United States	66	MRI	*28*	No; Funding from the National Heart, Lung, and Blood Institute and the Centers for Disease Control and

						Prevention; funding from On Steering committee for Alung Technologies.
Lang et al. 2021	Case Series; Retrospective, Single Center, Academic Hospital	Germany	116	MRI, CT	15.5 ± 19.6 (0–63)	No
Pantel et al. 2021	Cohort; Retrospective, Single Center, Academic Hospital	Germany	156	CT	16.4 ± 11.9 (7–40)	No
Marsh et al. 2021	Cohort, Retrospective, Single Center, Academic Hospital	England	24	MRI, CT	..	No
Hopkins et al. 2006	Cohort; Prospective, Single Center, General Hospital	US	15	CT	..	No
Hoesch et al. 2012	Cohort; Prospective, Single Center, Academic Hospital	US	68	MRI	..	..
Wongtangman et al. 2021	Cohort; Retrospective, Single Center, General Hospital	Israel	100	MRI	..	No; Philanthropic donations from Jeffrey and Judy Buzen to Matthias Eikermann
Thurnher et al. 2021	Cohort; Retrospective, Single Center, General Hospital	Austria	13	MRI	..	No; Open access funding provided by Medical University of Vienna
Holland et al. 2003	Cohort; Retrospective,	US	42	CT	..	No; Supported by the San Francisco

	Single Center, General Hospital					Injury Center through a grant from the Centers for Disease Control and Prevention (R49-CCR903697-07)
Wu et al. 2021	Cohort, Retrospective, Single Center, General Hospital	China	77	CT	..	No

Abbreviations: n°: number; US: United States; MRI: Magnetic Resonance Imaging; CT: Computed Tomography; ..: not reported; SOFA: Sequential Organ Failure Assessment; ARDS: Acute Respiratory Distress Syndrome; PaO2: partial pressure of oxygen; FiO2, fraction of inspired oxygen

Reasons for exclusion of the 206 studies during full text review were: not meeting ARDS diagnosis criteria (k=62), no MRI, CT or PET (k=44), case reports (k=53), results not stratified by ARDS (k=17), brain injuries were determined by study authors to be caused by neurological conditions such as traumatic brain injuries, thus ARDS was not causal in reported brain injuries (k=4), pediatric population included (k=2). Systematic review software Covidence was used as a reference manager and data extraction tool, which automatically removed 787 duplicate studies. An additional 3 studies were removed manually (see Figure 2.2) (Covidence Systematic Review Software, 2021).

Following all meta-analyses, a post-hoc sensitivity analysis was conducted to identify studies contributing to heterogeneity. Sensitivity analysis is a standard approach used in meta-analysis to determine how outlier studies affect the outcome of interest and how inclusion/exclusion of these outlier studies impact outcomes of interest (i.e. does removing an outlier study affect study conclusion). For the meta-analysis of ICH frequency, we included 17 COVID-19 ARDS and 7 non-COVID ARDS studies. For the meta-analysis of risk of developing ICH, 4 studies were included. For the frequency of subarachnoid hemorrhage (SAH) and intraparenchymal hemorrhage (IPH), and ischemic stroke in COVID-19 ARDS, 10, 16, and 12 studies respectively were included in the analysis (see Appendix C for additional analyses). Seven studies were included in the meta-analysis of non-COVID-19 ARDS ICH frequency and the analysis was limited to studies published from 2020 to 2022 to improve comparability, indicating pooled incidence of 12%.

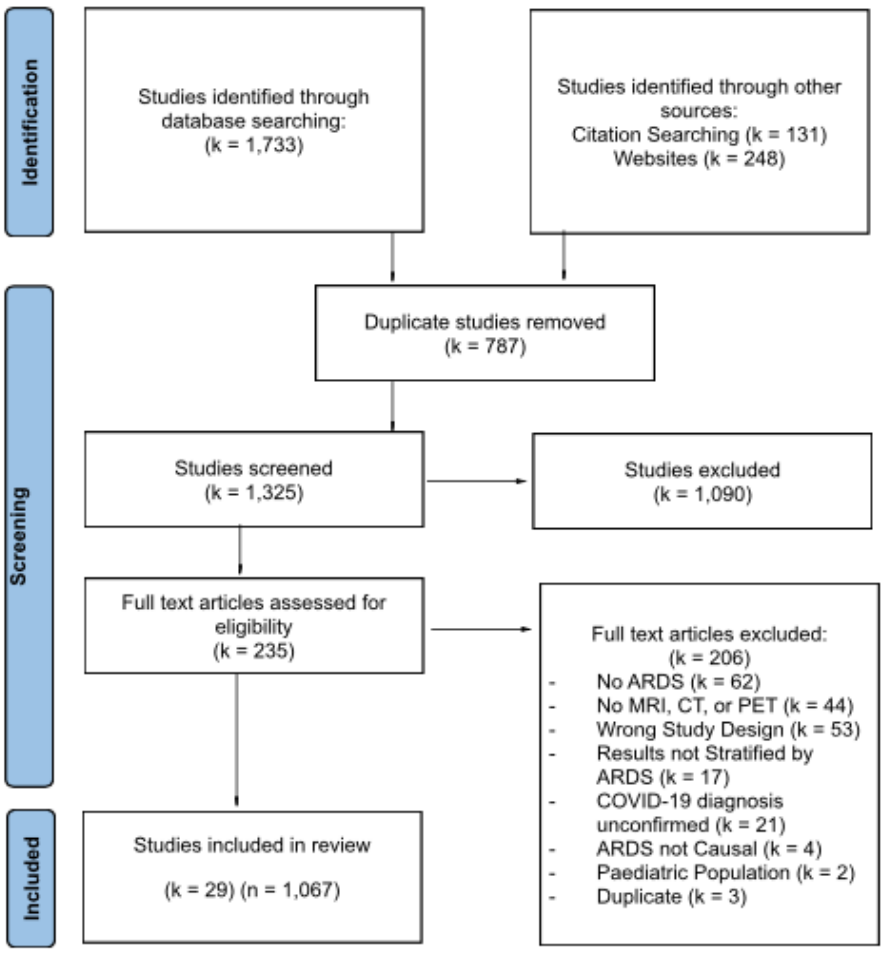


Figure 2.2: PRISMA Flow diagram depicting study eligibility criteria

2.5 Participant Characteristics

The age of COVID-19 ARDS patients ranged from 49.8 to 77 years with a mean age of 60.4 years and a standard deviation of 7.2. Non-COVID-19 ARDS patients had an average age of 49.4 years, with an age range of 47.1-70.9 years and a standard deviation of 10.6. Among COVID-19 ARDS patients, 143 were female, which represents 35% of the total number of patients. Among non-COVID-19 ARDS patients, 249 were female, representing 47.8% of the total number of patients. The etiology underlying non-COVID-19 ARDS was diverse; infectious causes made up 58.3% of cases and included pneumonia, viral pneumonia, pneumococcal pneumonia, influenza A, Legionella pneumonia, H1N1 viral pneumonitis, Mycoplasma pneumonia, metapneumovirus pneumonia, aspiration pneumonia, and HSV pneumonitis. Non-infectious causes accounted for

25% of cases and included massive pulmonary embolism, upper right lobe consolidation, tracheobronchial fistula, and life-threatening asthma. Systemic causes were responsible for 16.7% of cases and included sepsis, cardiogenic shock, brief PEA arrest, Klebsiella abscess, ANCA positive pulmonary renal syndrome, MOF, staph aureus septicemia, bilateral massive PE, cardiac arrest, leptospirosis with alveolar hemorrhage, streptococcal pneumonia, streptococcal sepsis, and pulmonary hemorrhage/renal syndrome (see Table 2.3). Of 173 reported patients in the COVID-19 ARDS group, 41.0% were referred for neuroimaging due to delayed awakening, 81.5% were referred due to neurological abnormalities, and 14.5% were imaged post-mortem. Comparatively, of 83 reported patients in the non-COVID-19 ARDS group, 18.1% were referred for neuroimaging due to delayed awakening, and 81.9% were referred due to neurological abnormalities.

2.6 Comorbidities, Risk Factors, and Interventions

Across the 29 studies, the COVID-19 ARDS group reported a mean duration of hospitalization of 22.9 days, mechanical ventilation of 14.9 days, and extracorporeal membrane oxygenation (ECMO) of 12 days. In comparison, across the 10 studies in the non-COVID-19 ARDS group, the mean duration of hospitalization was 16 days, mechanical ventilation of 23.2 days, and ECMO of 18.1 days (see Table 2.3). Average length of hospitalization, mechanical ventilation, non-invasive ventilation, and ECMO were similar between groups (see Table 2). In terms of interventions, the COVID-19 group had high utilization of anticoagulants (74.8%), dialysis (49.0%) and antiplatelet usage (23.6%). Prevalent comorbidities included diabetes (35.8%), chronic kidney injury (58.3%), heart disease (56.0%), liver disease (6.25%) and active malignancy (16.8%). Laboratory measurements were included in 10 out of the 29 articles, representing 34.5% of articles as summarized in Table 2. The laboratory parameters observed in COVID-19 patients include higher white blood cell counts (12.3 Tsd/µl), procalcitonin levels (0.8 ng/mL), fibrinogen levels (6.3 g/L), platelet counts (199.2), and hemoglobin levels (106 g/L). Additionally, COVID-19 patients exhibited lower glucose levels (130.5), lactate levels (1.5 mmol/L), and pH levels (7.3). Fibrinogen levels were elevated in COVID-19 ARDS patients (6.3 g/L). The COVID-19 ARDS group had a Simplified Acute Physiology (SAPS II) score of 46.7, an Acute Physiology and Chronic Health Evaluation (APACHE II) score of 24, a Sequential Organ Failure Assessment (SOFA) score of 9.8, a Charlson Comorbidity score of 2, and a Richmond Agitation Sedation Scale (RASS) score of -3.8. Pulmonary function measurements showed that the PaO_2/FiO_2 ratio was 111.3 mmHg,

PaO_2 levels were 72.9 mm Hg, $PaCO_2$ levels were 77.3 mm Hg, systolic blood pressure (SBP) was 111.5 mm Hg, diastolic blood pressure (DBP) was 55.5 mm Hg and mean arterial pressure (MAP) was 120.4 mm Hg. About 41.4% of patients in the COVID-19 ARDS group received ECMO therapy (see Figure 2.3).

Table 2.3: Patient Characteristics

	COVID-19 (n=390)		Non-COVID-ARDS (n=677)	
Variable	Outcome	Studies Reporting (n/k)	Outcome	Studies Reporting (n/k)
Age *(years) Mean (range)* ± *SD*	60.4 (49.8-77) ± 7.2	297/15	49.4 (47.1-70.9) ± 10.6	612/9
Sex *(female) n (%)*	143 (35.0)	390/19	249 (47.8)	636/9
Cause of ARDS *n (%)*	COVID-19-associated ARDS	390/19	Respiratory infections (24%): Cystic fibrosis, Influenza, Pneumonia, H1 N1 Viral pneumonitis Respiratory diseases (48%): Sarcoidosis, Pneumonia, Congestive cardiomyopathy Non-respiratory diseases (28%): Hemorrhagic shock, Heart failure	179/5
Ventilation	Outcome	Studies Reporting (n/k)	Outcome	Studies Reporting (n/k)
Duration of Non-Invasive Ventilation *(days)*	17	9/1	..	0/0
Duration of Invasive Ventilation *(days) Mean (range)* ± *SD*	14.9 (4-30) ± 8.4	308/15	23.2 (0.5-31) ± 14.6	355/4
PaO_2/FiO_2 Ratio *Mean (range)* ± *SD*	111.3 ± 46.0	112/4	124.7 ± 65.2	442/7
Prone Positioning, *n (%)*	13 (63.9)	21/2	56 (56.0)	100/1
ECMO, *n (%)*	101 (41.4)	215/9	277 (79.3)	373/4
ECMO Duration *(days) Mean (range)* ± *SD*	12.0 (3-89) ± 7.6	215/9	8.1 (0-100) ± 5.4	373/4
Sedation Depth and Agents	Outcome	Studies Reporting (n/k)	Outcome	Studies Reporting (n/k)
RASS, *Mean (range)* ± *SD*	-3.8 (-5-0) ± 1.0	75/2	−3.4 (−5–0) ± 1.6	116/1
Propofol, *n (%)*	29 (82.7)	40/2	20 (20.0)	20/1
Midazolam, *n (%)*	5 (21.7)	40/2	12 (12.0)	12/1

Dexmedetomidine, *n (%)*	1 (8.3)	12/1	10 (10.0)	10/1
Opioids, *n (%)*	9 (49.4)	2	12 (12.0)	12/1
Severity of Illness Scores	Outcome *Mean (range) ± SD*	Studies Reporting (n/k)	Outcome *Mean (range) ± SD*	Studies Reporting (n/k)
SAPS II	46.7 (38-63) ± 2.1	85/3	47.7 (24-88) ± 1.2	224/2
APACHE II	24 (20–29)	36/2	20.7 (20–30) ± 4.7	192/3
SOFA	9.8 (2-17) ± 2.2	123/3	11.8 (2-19) ± 0.5	349/3
Charlson Comorbidity Index	2 (0-2) ± 1.4	84/2	3 (0-4) ± 2.1	2562
Baseline Laboratory Results	Outcome *Mean (range) ± SD*	Studies Reporting (n/k)	Outcome *Mean (range) ± SD*	Studies Reporting (n/k)
WBC (Tsd/µll)	12.3 ± 4.7	147/6	16.2	116/1
Hemoglobin (g/L)	106 ± 22.2	176/6	101.5 ± 3.5	272/2
Platelets (109/uL)	199.2 ± 94.2	186/7	77 ± 22.3	349/3
Procalcitonin (ng/mL)	0.8 ± 0.6	66/2	16	116/1
Fibrinogen (g/L)	6.3 ± 1.8	123/5	3.2 ± 0.08	233/2
Lactate (mmol/L)	1.5 ± 0.6	96/3	3.1 ± 2.5	180/2
pH	7.3 ± 0.2	93/3	7.4 ± 0.06	401/4
Comorbidities	Outcome *n (%)*	Studies Reporting (n/k)	Outcome *n (%)*	Studies Reporting (n/k)
Diabetes	60 (35.8)	165/12	37 (19.5)	211/3
Heart Disease	87 (56.0)	137/10	13 (8.4)	148/3
Lung Disease	52 (36.5)	148/10	66 (49.0)	183/4
Kidney Disease	92 (58.3)	184/11	41 (29.0)	235/4
Liver Disease	2 (6.25)	50/3	34 (11.2)	341/5
Cancer	11 (16.8)	91/5	32 (12.7)	250/3
Treatments	Outcome *n (%)*	Studies Reporting (n/k)	Outcome *n (%)*	Studies Reporting (n/k)
Antiplatelets	31 (23.6)	114/5	30 (10.7)	341/3
Anticoagulants	181 (74.8)	263/13	50 (16.3)	338/3
Corticosteroids	15 (36.9)	54/4	..	0/0
Antivirals	57 (88.5)	62/5	..	0/0
Antibiotics	27 (62.7)	43/4	..	0/0
Dialysis	85 (49.0)	206/9	84 (22.3)	415/4

Data is presented as mean average. Percentages (%) were calculated as weighted averages. Range is included in brackets. Abbreviations: ..: the study did not report the value; n: number of patients

Utilization of anticoagulants, dialysis and antiplatelets in the ARDS group was 16.3% 22.3%, and 10.7% respectively. Prevalence of comorbidities differed, including diabetes as 19.5%, chronic kidney injury as 29.0%, heart disease as 8.4%, liver disease as 11.2%, and active malignancy at 12.7%. The reported laboratory parameters for non-COVID-19 ARDS patients included higher levels of white blood cell counts (16.2 Tsd/µll) and procalcitonin (16 ng/mL), but lower levels of fibrinogen (3.2 g/L), platelets (77), and hemoglobin (101.5 g/L). The non-COVID-19 ARDS group had a SAPS II score of 47.7, APACHE II score of 20.7, SOFA score of 11.8, Charlson Comorbidity Score of 3, and RASS score of -3.4. Pulmonary function measures included a PaO_2/FiO_2 ratio of 124.7 mmHg, PaO_2 levels of 67.3 mm Hg, $PaCO_2$ levels of 44.7 mm Hg, systolic blood pressure (SBP) of 124.5 mm Hg, diastolic blood pressure (DBP) of 55.5 mm Hg, and mean arterial pressure (MAP) of 87 mm Hg. Additionally, 79.3% of patients in the ARDS group received ECMO therapy (see Table 2.3).

In the COVID-19 ARDS group, 59.0% of studies utilized MRI, 21.3% of studies utilized CT, and 19.7% of studies utilized both MRI and CT. Comparatively, in the non-COVID-19 ARDS group, CT was utilized in 46.2% of studies, MRI was utilized in 37.4% of studies, , and both MRI and CT were utilized in 16.8% of studies. There is a statistically significant preference to use MRI in the COVID-19 ARDS group, as indicated by a Chi-Squared test ($p < 0.0001$). In comparison, there is no statistically significant preference to use MRI or CT for non-COVID-19 ARDS patients ($p=0.84$). Neuroimaging indications also differed between groups, including delayed awakening reported in 41.0% of studies with available data in the COVID-19 ARDS group versus 18.1% in the non-COVID-19 ARDS group, neurological abnormalities in 81.5% and 81.9% respectively, and post-mortem neuroimaging in 14.5% and 2.4% respectively. In the COVID-19 group, WMH were found in 45.2% of patients, while ICH was observed in 32.5% of cases, predominantly IPH (27.1%), subarachnoid hemorrhage was found in 21.1% of patients, and subdural/epidural hemorrhage (SDH/EDH) was found in 7.5%. Microhemorrhages were present in 37.4% of patients, and ischemic stroke was found in 13.0% of cases. The damage localized to white matter areas was more common in COVID-19 ARDS patients and included ICH (13.9%), microhemorrhages (18.0%), and ischemic stroke (2.3%). COVID-19 ARDS patients were also

more likely to have cerebral microhemorrhages that particularly impacted callosal structures (33.6%), and WMH were reported in 41.8% of patients. The non-COVID-19 ARDS group exhibited differing frequencies of brain injuries, such as ICH (20.8%), WMH (13.9%), SDH/EDH (7.8%), subarachnoid hemorrhage (7.2%), microhemorrhages (7.2%), and ischemic stroke (12.5%).

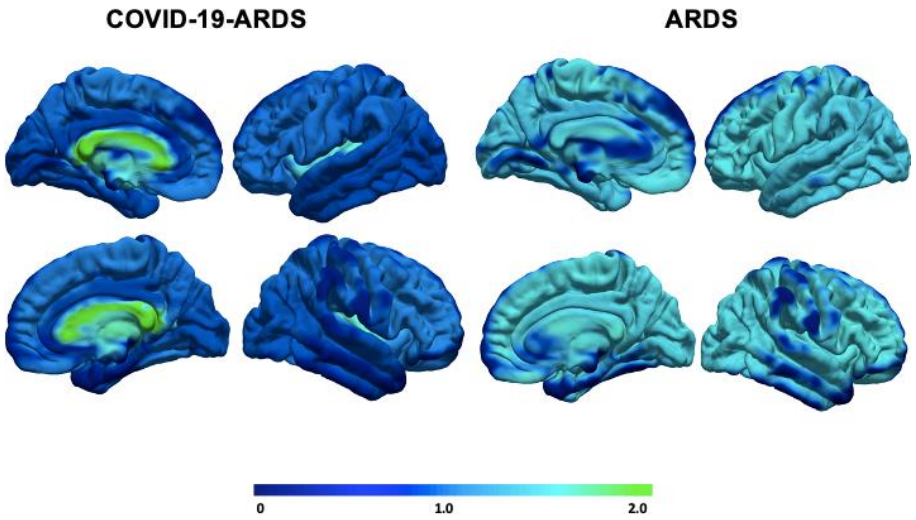


Figure 2.3: Surface-rendered projections of pooled neuroimaging findings in COVID-19 and ARDS across types of brain injuries

2.7 Outcomes of Meta-Analysis

A meta-analysis was then conducted to further investigate brain injuries in the COVID-19 ARDS group as compared to the non-COVID-19 ARDS group. A post-hoc sensitivity analysis was then conducted to remove outliers and influential studies. This analysis identified Helms 2020 as an outlying study and Wongtangman 2021 as a study contributing greatly to heterogeneity. After removing these studies, a meta-analysis found a very similar pooled proportion of 31% (95% CI 24% to 40%), with decreased heterogeneity to I^2 of 47%. To make the results of the meta-analysis of intracerebral hemorrhage more comparable to the COVID-19 ARDS meta-analysis, studies published from 2020 to 2022 were included. Heterogeneity was significant with all studies included (I^2=82%), decreasing to more acceptable levels once limited (I^2=57%). The pooled

incidence of ICH for studies assessing patients was 12% (95% CI 8% to 18%) (see Figure 2.4) (See Appendix C for all meta-analyses conducted with available data).

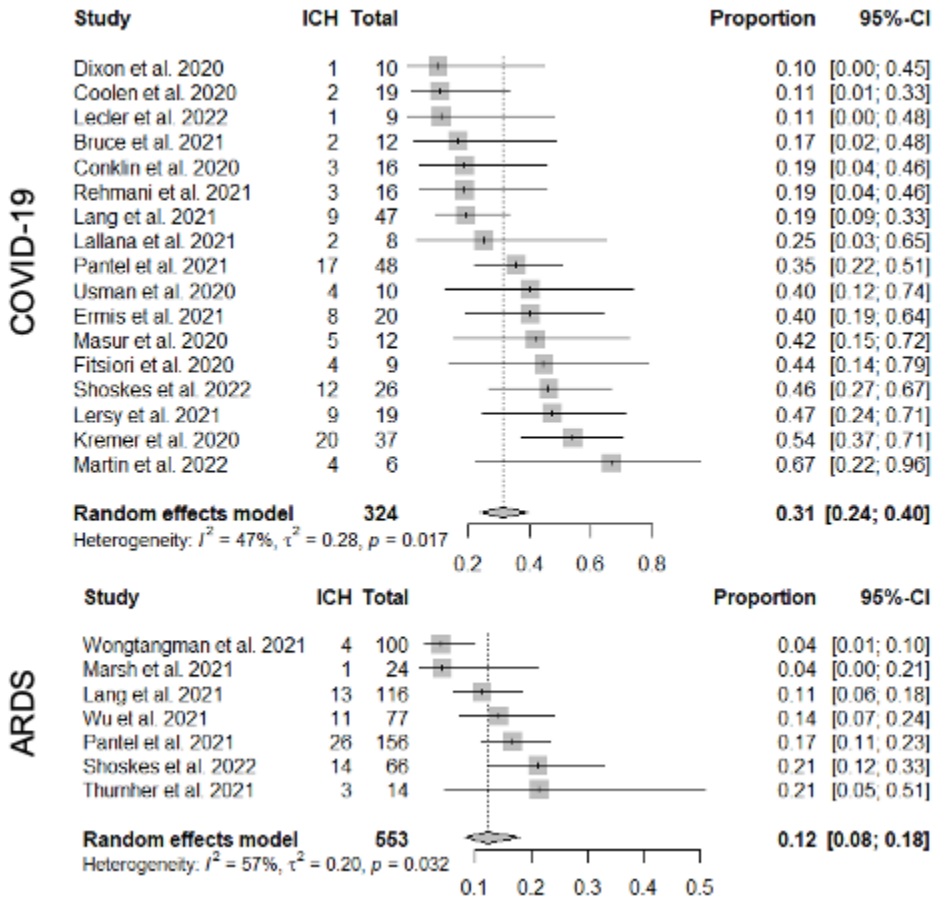


Figure 2.4: Meta-analysis of COVID-19 ARDS and non-COVID-19 ARDS ICH frequency indicating pooled proportions

A comparison of the risk of ICH for COVID-19 and patients was possible for only four studies. The risk of ICH was found to be twofold higher in COVID-19 patients, with a pooled risk ratio of 2.09 (95% CI 1.68 to 2.59). This result was statistically significant, as the 95% confidence interval did not cross 1.00 (no effect), and the p-value was 0.0017. There was no between study heterogeneity (I^2=0%) for this analysis (see Figure 2.5).

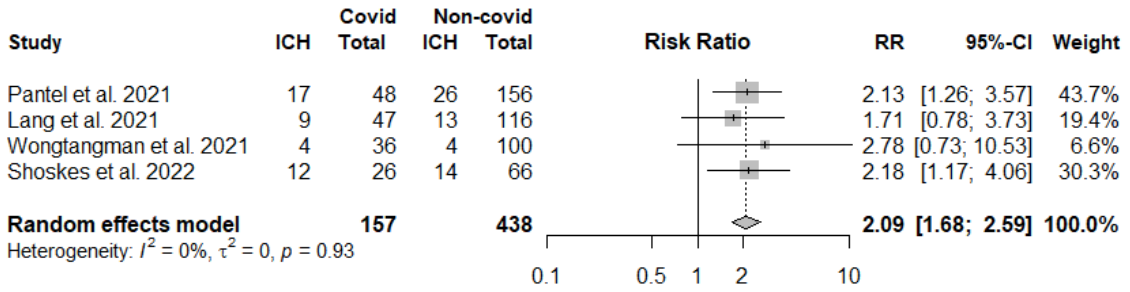


Figure 2.5: Risk for developing ICH in COVID-19 ARDS versus non-COVID-19 ARDS

2.8 Discussion

In this review and meta-analysis involving 390 patients with COVID-19 ARDS and 677 patients with non-COVID-19 ARDS of other causes, we found differences in the type, pattern and location of brain injuries, in critically ill patients with COVID-19 ARDS versus non-COVID-19 ARDS patients which may implicate distinct pathophysiology and functional outcomes. Our results indicate the likelihood of developing ICH was found to be 31% in COVID-19 ARDS patients, whereas for non-COVID-19 ARDS patients, the pooled incidence was 12%. The study suggested that the risk of ICH in COVID-19 patients was twice that of patients, and this difference was statistically significant. The pooled risk ratio for the four studies which compared COVID-19 ARDS to non-COVID-19 ARDS was 2.09, and this difference was statistically significant. These results suggest that the risk of ICH in COVID-19 ARDS patients is twice that of non-COVID-19 ARDS patients. COVID-19 ARDS patients showed a higher percentage of brain injury localized to white matter areas, including intracerebral hemorrhage, microhemorrhages, and ischemic stroke. Cerebral microhemorrhages particularly affected callosal structures, and WMH were reported to a greater extent.

Frequency of ICH in a recent analysis of COVID-19 registry data was indicated to be 48 (0.2%) of 21,483 patients, 90% of whom were in the ICU, nominally older, predominantly male (73% versus 54%), and had more vascular risk factors (Leasure et al. 2021). Patients presented an unusual pattern of damage preferentially targeting white matter, in contrast to neuroimaging findings acquired from non-COVID-19 ARDS patients. Several studies have reported evidence of white matter injury in COVID-19 patients, particularly those with severe respiratory symptoms. A study published in the journal Radiology in June 2021 found that COVID-19 patients with severe

respiratory symptoms had a higher prevalence of white matter abnormalities on MRI compared to patients with mild or moderate symptoms, which may relate to incidence and severity of illness (Kandemirli et al. 2020). The study also found a correlation between the severity of respiratory symptoms and the extent of white matter injury Another study published in the journal Annals of Neurology in November 2020 reported that COVID-19 patients who developed neurological symptoms had evidence of white matter injury on MRI, including abnormalities in the corpus callosum (Kremer et al. 2021). The COVID-19 patient group included in this review presented with increased prevalence of several comorbidities, risk factors, and advanced age, which may increase the risk for developing critical illness and associated sequalae following COVID-19 infection. It is important to acknowledge that the neuroimaging outcomes documented in this patient group may relate to propensity for developing a more severe clinical course of illness rather than instead being directly related to COVID-19 infection itself. (Kremer et al. 2021). The protracted course of COVID-19 illness, complicated clinical course and treatments, and pre-existing comorbidities and risk factors limit conclusions regarding causal relationships between COVID-19 infection and brain injuries seen on neuroimaging. More data are needed to determine the impact of the SARS-CoV-2 virus in the brain outcomes documented in the COVID-19 ARDS patient population.

These results suggest that patients with COVID-19 ARDS may have a higher risk of neurological complications, including cognitive impairment and delirium, compared to those with non-COVID-19 ARDS. Helms et al. found the incidence of delirium in COVID-19 to be significantly higher compared to ARDS patients, indicating a difference in acute brain dysfunction (Helms et al. 2020). There seems to be a similar effect in patients who have recovered from mild COVID-19, with a recent cohort study finding that these patients had lasting neurocognitive deficits that included impaired short-term memory, attention, and concentration. A meta-analysis found that impaired concentration and attention were common in 19.9% and impaired memory in 18.9% of patients after recovery of mild COVID-19 (Woo et al. 2020). It remains unclear if impairments relate to the incidence of illness or if COVID-19 may itself contribute risk for developing complications. A recent retrospective cohort study examined the health records from 68 health organizations and collected data from 410,748 participants with a past documented incidence of COVID-19 infection and compared them to 5,834,534 control group participants without a past documented COVID-

19 infection. They found participants with a documented past COVID-19 infection to be at higher risk for a new AD diagnosis within 360 days after the initial COVID-19 diagnosis, especially those aged 85 years and older (Wang et al. 2022). It remains unclear whether causal links between COVID-19 and the incidence of neurological abnormality exists, or if comorbidities, age, or other risk factors may influence results or accelerate pre-existing illness. Patients who have experienced the most severe forms of COVID-19 infection were susceptible to both direct and indirect brain injury (Wang et al. 2022). By learning about the type, frequency and location of brain injury, we may start to better understand the pathophysiology underlying these impairments. If the long-term effects of COVID-19 on the brain are not well understood, it may be difficult to anticipate and mitigate the cognitive and functional consequences of future pandemics.

While the results of our review provide novel insights, they are limited by several key factors. Firstly, location of brain injury was inconsistently and relatively underreported across the included studies. There was a clear difference in reporting of findings between ARDS and COVID-19 publications, such that the latter included more detailed and comprehensive neuroimaging results which may contribute to underreporting in ARDS. Secondly, there was a lack of comprehensive paraclinical tests in many of the studies and not all patients had the same set of clinical tests performed. Thirdly, obtaining in vivo neuroimaging, especially MRI, in critically ill COVID-19 patients, with high infectious potential is limited due generally to contraindications to imaging critically ill patients, leading to underestimation of neurological involvement in these patients. Neuroimaging was typically acquired in subsets of patients frequently recruited selectively rather than being subject to randomization procedures. Finally, patients included in this review received multiple forms of treatments and medications which may confer heightened vulnerability to brain damage, including ECMO, which is independently associated with brain injury and presents an important confounding factor (Combes et al., 2018; Matthay et al., 2019).

2.9 References

1. Abate SM, Ahmed S, Mantfardo B, Basu B. (2022). Rate of Intensive Care Unit admission and outcomes among patients with coronavirus: A Review and Meta-analysis. *PLoS ONE*, 15(7).
2. Almaghaslah D, Kandasamy G, Almanasef M, Vasudevan R, Chandramohan S. (2020). Review on the coronavirus disease (COVID-19) pandemic: its outbreak and current status. *Intl J Clin Practice,* 74(11), e13637.
3. Arabi YM, Harth A, Hussein J. (2015). Severe neurologic syndrome associated with Middle East respiratory syndrome coronavirus (MERS-CoV). *Infection,* 43, 495–501.
4. The ARDS Definition Task Force. (2012). Acute Respiratory Distress Syndrome: The Berlin Definition. *JAMA*, 307(23), 2526–2533.
5. Bain A, Yang W, Shah F. (2021). COVID-19 versus Acute Respiratory Distress Syndrome: Comparison of Demographics, Physiologic Parameters, Inflammatory Biomarkers, and Clinical Outcomes. *Ann Am Thorac Soc,* 18(7), 1202–1210.
6. Brault, C., Zerbib, Y., Kontar, L., Fouquet, U., Carpentier, M., Metzelard, M., Soupison, T., De Cagny, B., Maizel, J., Slama, M. (2020). COVID-19- versus non-COVID-19-related acute respiratory distress syndrome: differences and similarities. *Am J Respir Crit Care Med*, 202, 1301–1304.
7. Bruce S, Kahan J, Huq T. (2021). Missed cerebrovascular events during prolonged sedation for COVID-19 pneumonia. *J Clin Neurosci,* 86, 180–18.
8. Coolen T, Lolli V, Sadeghi N. (2020). Early postmortem brain MRI findings in COVID-19 non-survivors. *Neurology,* 95(14)*,* e2016–e2027.
9. Conklin J, Frosch MP, Mukerji SS. (2021). Susceptibility-weighted imaging reveals cerebral microvascular injury in severe COVID-19. *J Neurol Sci,* 421*,* 117308.
10. Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org.
11. Czajkowska-Malinowska M, Kania A, Kuca P. (2020). Treatment of acute respiratory failure in the course of COVID-19. Practical hints from the expert panel of the Assembly of Intensive Care and Rehabilitation of the Polish Respiratory Society. *Adv Respir Med*, 88(3), 245–266.

12. Dixon L, McNamara C, Gaur P. (2020). Cerebral microhaemorrhage in COVID-19: a critical illness related phenomenon? *Stroke Vasc Neurol,* 5(4), 315–322
13. Dong E, Du H, Gardner L. (2020). An interactive web-based dashboard to track COVID-19 in real time. *Lancet Infectious Disease,* 20(5), 533–543.
14. El-Solh A, Meduri U, Lawson Y, Carter M, Mergenhagen K. (2021). Clinical Course and Outcome of COVID-19 Acute Respiratory Distress Syndrome: Data From a National Repository. *J Intensive Care Med*, 36(6), 664–672.
15. Ferrucci R, Dini M, Groppo E. (2021). Long-Lasting Cognitive Abnormalities after COVID-19. *Brain Sci,* 11, 235.
16. Fitsiori A, Pugin D, Thieffry C, Lalive P, Vargas MI. (2020). COVID-19 is Associated with an Unusual Pattern of Brain Microbleeds in Critically Ill Patients. *Amer Soc Neuroimaging,* 30(5)*,* 593–597.
17. Fischl B, Salat DH, Busa E. (2002). Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron,* 33, 341–355.
18. Garcia M, Barreras PV, Pardo CA. (2021). Cerebrospinal fluid in COVID-19 neurological complications: Neuroaxonal damage, anti-SARS-Cov2 antibodies but no evidence of cytokine storm. *J Neurol Sci,* 427, 117517.
19. Gibson PG, Qin L, Puah SH. (2020). COVID-19 acute respiratory distress syndrome (ARDS): clinical features and differences from typical pre-COVID-19 ARDS. Med J, 213(2):54-56
20. Gonçalves B, Righy C, Kurtz P. (2020). Thrombotic and Hemorrhagic Neurological Complications in Critically Ill COVID-19 Patients. *Neurocritical Care,* 33(2), 587–590
21. Hariri LP, North CM, Shih AR. (2021). Lung histopathology in coronavirus disease 2019 as compared with severe acute respiratory syndrome and H1N1 influenza: a systematic review. *Chest,* 159(1), 73–84
22. Helms J, Kremer S, Merdji H. (2020). Delirium and encephalopathy in severe COVID-19: a cohort analysis of ICU patients. *Critical Care,* 24(1), 491.
23. Hoesch RE, Lin, E. Young, M. Gottesman, R.F. Altaweel, L. Nyquist, P.A. Stevens, R.D. (2021). Acute lung injury in critical neurological illness. *Critical Care Medicine,* 40(2), 587–93.

24. Holland MC, Mackersie RC, Morabito D. (2003). The Development of Acute Lung Injury Is Associated with Worse Neurologic Outcome in Patients with Severe Traumatic Brain Injury. *J Trauma,* 55, 106–111.
25. Hopkins RO, Suchyta MR, Been K, Jackson JC. (2016) Critical illness acquired brain injury: Neuroimaging and complications for rehabilitation. *Rehab Psychol,* 61(2), 151–164.
26. Hopkins RO, Gale SD, Weaver LK. (2006). Brain atrophy and cognitive impairment in survivors of acute respiratory distress syndrome. *Brain Injury,* 20(3), 263–271.
27. Huang Y, Tan C, Wu J. (2020). Impact of coronavirus disease 2019 on pulmonary function in early convalescence phase. *Respir Research,* 21, 163.
28. Karadaş O, Oztürk B, Sonkaya AR. (2020). A prospective clinical study of detailed neurological manifestations in patients with COVID-19. *Neurol Sci,* 41, 1991–1995.
29. Kas A, Soret M, Pyatigoskaya N. (2021). The cerebral network of COVID-19-related encephalopathy: a longitudinal voxel-based 18F-FDG-PET study. *Eur J Nucl Med Mol I,* 48(8), 2543–2557.
30. Katala S, Balakrishnanb S, Gholamrezanezha A. (2021). Neuroimaging and neurologic findings in COVID-19 and other coronavirus infections: A Review in 116 patients. *J Neuroradiology,* 48(1)*,* 43–50.
31. Kwong KCN, Mehta PR, Shukla G, Mehta AR. (2020). COVID-19, SARS and MERS: A neurological perspective. *J Clin Neurosci,* 77, 13–16.
32. Kremer S, Lersy F, de Seze J. (2020). Brain MRI Findings in Severe COVID-19: A Retrospective Observational Study. *Radiology,* 297(2), E242–E251.
33. Lallana S, Chen A, Requena M. (2021). Posterior reversible encephalopathy syndrome (PRES) associated with COVID-19. *J Clin Neuroscience,* 88, 108–112.
34. Lang CN, Dettinger JS, Berchtold-Herz M. (2021). Intracerebral Hemorrhage in COVID-19 Patients with Pulmonary Failure: A Propensity Score-Matched Registry Study. *Neurocritical Care,* 34(3), 739–747.
35. Latronico N, Peli E, Calza S. (2022). Investigators, Physical, cognitive and mental health outcomes in 1-year survivors of COVID-19-associated ARDS. *Thorax*, 77, 300–303.

36. Leasure AC, Khan YM, Lyer R. (2021). Intracerebral Hemorrhage in Patients With COVID-19 An Analysis From the COVID-19 Cardiovascular Disease Registry. *Stroke,* 52, e321–e323.
37. Lecler A, Cotton F, Lersy F, Kremer S, Héran F. (2021). Abnormal MRI findings of the orbital or visual pathways in patients with severe COVID-19: Observations from the French multicenter COVID-19 cohort. *J Neuroradiology*, 48(5), 331–336.
38. Lecler A, Cotton F, Lersy F, Kremer S, Heran F. (2022). Ocular MRI Findings in Patients with Severe COVID-19: A Retrospective Multicenter Observational Study. *Radiology,* 302(1), E226–E229.
39. Lersy F, Willaume T, Brisset JC. (2021). Critical illness-associated cerebral microbleeds for patients with severe COVID-19: etiologic hypotheses. *J Neurology,* 268(8), 2676–2684.
40. Li J, Xiao L, He D, Luo Y, Sun H. (2021). Mechanism of White Matter Injury and Promising Therapeutic Strategies of MSCs After Intracerebral Hemorrhage. *Front Aging Neurosci,* 13.
41. Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH. (2003). An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *Neuroimage,* 19(3)*,* 1233–9.
42. Maldjian JA, Laurienti PJ, Burdette JH. (2004). Precentral gyrus discrepancy in electronic versions of the Talairach atlas. *Neuroimage,* 21(1), 450–5.
43. Mao JH, Wang M, Wang M. (2020). Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. *JAMA Neurol,* 77(6), 683–690.
44. Marsh LC, Leach RM, Blane J. (2021). Long-term cognitive and psychiatric outcomes of acute respiratory distress syndrome managed with Extracorporeal Membrane Oxygenation. *Respir Med,* 183, 106419–106419.
45. Martin MGM, Paes VR, Cardoso EF. (2022). Postmortem brain 7T MRI with minimally invasive pathological correlation in deceased COVID-19 subjects. *Insights into Imaging,* 13(1), 7.
46. Morelli N, Johnson NF, Cassity EP. (2021). Feasibility of Contrasting Brain Connectivity Patterns in Cognitive and Motor Cerebral Networks to Clinical Outcomes in Patients Surviving Acute Respiratory Failure: A Pilot Study. *Cureus,* 13(9), e17785.

47. Nadkarni N, Studenski S, Perera S. (2013). White Matter Hyperintensities, Exercise and Improvement in Gait Speed: Does the Type of Gait Rehabilitation Matter? *J Amer Ger Soc,* 61(5).
48. Najt B, Richards H, Fortunea G. (2021). Brain imaging in patients with COVID-19: A Review. *Brain Behaviour Immune Health,* 16, 100290.
49. Nemer SN, Caldeira JB, Azeredo LM. (2011). Alveolar recruitment maneuver in patients with subarachnoid hemorrhage and acute respiratory distress syndrome: a comparison of 2 approaches. *J Critical Care,* 26(1), 22–7
50. Page MJ, McKenzie JE, Bossuyt PM. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Syst Rev*, 10(1), 89
51. Pantel T, Roedl K, Jarczak D. (2022). Association of COVID-19 with Intracranial Hemorrhage during Extracorporeal Membrane Oxygenation for Acute Respiratory Distress Syndrome: A 10-Year Retrospective Observational Study. *J Clinical Medicine,* 11(1), 28–28.
52. Petridis AK, Doukas AK, Maslehaty H, Mahvash M, Barth H, Mehdorn HM. (2020). The effect of lung-protective permissive hypercapnia in intracerebral pressure in patients with subarachnoid haemorrhage and ARDS. A retrospective study. *Acta Neurochirurgica,* 152(12), 2143–5.
53. Rehmani R, Segan S, Maddika SR, Lei YW, Broka A. (2021). Spectrum of neurologic & neuroimaging manifestation in COVID-19. *Brain, Behavior, & Immunity – Health,* 13(101759062), 100238.
54. Rezoagli E, McNicholas BA, Madotto F. (2021). Presence of comorbidities alters management and worsens outcome of patients with acute respiratory distress syndrome: insights from the LUNG SAFE study. *Ann Intensive Care,* 12(42).
55. Riech S, Kallenberg K, Moerer O. (2015). The Pattern of Brain Microhemorrhages after Severe Lung Failure Resembles the One Seen in High-Altitude Cerebral Edema. *Critical Care Medicine,* 43(9), e386–e389.
56. Rogers J, Chesney E, Oliver D. (2020). Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a Review and meta-analysis with comparison to the COVID-19 pandemic. *Lancet Psychiatry,* 7(7), 611–627

57. R Core Team. (2021). R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing.
58. Sanyaolu A, Okorie C, Marinkovic AP. (2020). Comorbidity and its Impact on Patients with COVID-19. *Comput Clin Med*, 2(8), 1069–1076.
59. Saad M, Omrani AS, Baig K, Bahloul A, Elzein F, Matin MA. (2014). Clinical aspects and outcomes of 70 patients with Middle East respiratory syndrome coronavirus infection: a single-center experience in Saudi Arabia. *Intl J Infectious Dis,* 29, 301–306.
60. Shoskes A, Huang M, Gedansky A. (2020). MRI of Cerebrovascular Injury Associated With COVID-19 and Acute Respiratory Distress Syndrome: A Matched Case-Control Study. *Critical Care Medicine,* 50(11), 1638–1643.
61. Spudich S, Nath A. (2022). Nervous system consequences of COVID-19. *Science,* 375, 267–269.
62. Taquet M, Geddes JR, Husain M, Luciano S, Harrison PJ. (2021). 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. *Lancet Psychiatry*, 8(5), 416–427.
63. Tay MRJ, Ong PL, Puah SH, Tham SL. (2021). Acute Functional Outcomes in Critically Ill COVID-19 Patients. *Intensive Care Medicine and Anesthesiology,* 18(7), 615997.
64. Tekkök SB, Ye Z, Ransom BR. (2007). Excitotoxic mechanisms of ischemic injury in myelinated white matter. J Cereb Blood Flow Metab, 27(9):1540-52.
65. Thurnher MM, Boban J, Röggla M, Staudinger T. (2021). Distinct pattern of microsusceptibility changes on brain magnetic resonance imaging (MRI) in critically ill patients on mechanical ventilation/oxygenation. *Neuroradiology,* 63, 1651–1658.
66. Ummehan E, Rust M, Bungenberg J, (2021). Neurological symptoms in COVID-19: a cross-sectional monocentric study of hospitalized patients. *Neurological Research and Practice,* 3(1), 17.
67. Umapathi T, Kor AC, Venketasubramanian N, Lim CCT. (2004). Large artery ischaemic stroke in severe acute respiratory syndrome (SARS). *J Neurol,* 251(10), 1227–31.
68. Usman AA, Han J, Acker A. (2020). A Case Series of Devastating Intracranial Hemorrhage During Venovenous Extracorporeal Membrane Oxygenation for COVID-19. *J Cardiothoracic Vascular Anesthesia,* 34(11), 3006–3012.

69. Wang, L., Davis, P.B., Volkow, N.D., Berger, N.A., Kaelber, D.C., Zu, Rong.. (2022). Association of COVID-19 with New-Onset Alzheimer's Disease. *J Alzheimers Dis*, 89, 411-414
70. Wongtangman K, Santer P, Wachtendorf LJ, (2021). Association of Sedation, Coma, and In-Hospital Mortality in Mechanically Ventilated Patients With Coronavirus Disease 2019-Related Acute Respiratory Distress Syndrome: A Retrospective Cohort Study. *Critical Care Medicine,* 9(9), 1524–1534.
71. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med, 7, 934-943.
72. You Q, Yang Y, Hu H. (2022). White Matter Hyperintensities and Functional Outcomes in Patients With Cerebral Hemorrhage: A Review and Meta-Analysis. *Front Neurol,* 13, 820012.
73. Ziehr D, Alladina J, Petri CR. (2020). Respiratory Pathophysiology of Mechanically Ventilated Patients with COVID-19: A Cohort Study. *Am J Respir Crit Care Med,* 201(12), 1457–1429.

Chapter 3

3 Evaluating the impact of intensity normalization on automated quantification of White Matter Hyperintensities

WMH are commonly found in healthy older adults on T2-weighted brain MRI and their prevalence increases with age. WMH are commonly associated with various risk factors such as hypertension, aging, diabetes, and smoking, causing significant structural changes in small vessels of the brain. WMH can lead to cognitive decline, mild cognitive impairment, dementia, stroke, and gait disturbances. Given the results of the systematic review described in Chapter 2, indicating damage to white matter in COVID-19 ARDS, we have focused on examining and validating accurate and efficient segmentation methods for WMH for automated quantification of lesion loads and volumes on MRI.

Manual segmentation by trained experts is time-consuming and can face reliability challenges. Automated segmentation methods including emerging approaches based on machine learning techniques are promising, but may be biased by image preprocessing steps, particularly intensity normalization. Unlike computed tomography (CT) or positron emission tomography (PET) where measurements are in absolute physical units, structural MRI scans used in quantifying WMH are arbitrary units that differ between scans, individuals, and scanners, making it challenging to compare image intensities to derive WMH index. By scaling the distribution of image intensities across subject/scans/scanners, intensity normalization is crucial in quantitative MRI for standardizing image intensities to enhance image registration and fusion, facilitate group comparisons enable accurate quantitative analysis, which improves biomarker detection (Shinohara et al. 2014). While many intensity normalization methods exist to improve MRI data quality, there remains little evidence as to which methods are most efficacious in improving subsequent segmentation of WMH. Our aim is to evaluate the performance of five different intensity normalization methods and assess their impact on automated WMH segmentation and subsequent quantification (Fooroshani et al. 2022). The robustness of intensity normalization methods was evaluated in a cohort of stroke patients with WMH of presumed vascular origin who are part of an ongoing post-stroke cognitive impairment (PSCI) study. The optimal intensity normalization was then used in pre-preprocessing MRI data for automated segmentation using the

HyperMapp3r deep learning tool (Fooroshani et al., 2022). This analysis pipeline will ultimately be applied to MRI data acquired from patients with COVID-19 and ARDS enrolled in the ongoing Neuro-SedAting with Volatile Anesthetics (SAVE)-ICU study (n=30).

3.1 Clinical Motivation for Assessing WMH

WMH are foci of hyperintensity detected on anatomical MRI and are of presumed vascular origin as a manifestation of small vessel ischemic disease. WMH are a common incidental finding in healthy older adults, with prevalence rates ranging between 39 and 96% (Prins et al, 2015; Wardlaw et al, 2013a; Wardlaw et al, 2015). While WMH are common in asymptomatic individuals, their prevalence increases with age from approximately 10% to 20% in those approximately 60 years old to close to 100% in those older than 90 years (Garde et al, 2000; Smith et al, 2017; Ylikoski et al, 1995). WMH can accumulate in the brain at a rate of 0.1 to 2.2 mL/year, the presence of which increases the likelihood of developing mild cognitive impairment (MCI), dementia, stroke, and gait disturbances (Jochems et al, 2022; van Leijsen et al, 2017). Aging and hypertension are the main predictors of WMH, and genome-wide association studies have identified associations with genes involved in blood pressure regulation, particularly in those with sustained exposure to vascular risk factors including hypertension (Hirose et al, 2011; Persyn et al, 2020), chronic kidney disease (Marini et al, 2020; Rensma et al, 2018), diabetes, and dyslipidemia (Lin et al, 2017; Wardlaw et al., 2013a; Wardlaw et al., 2013b). Other risk factors associated with WMH include hypercholesterolemia, smoking, carotid artery disease, and heart failure (Shao et al, 2019; Wardlaw et al, 2013a). These risk factors cause significant structural changes in the small vessels of the brain including narrowing of the lumen and loss of smooth muscle cells, which ultimately result in impaired vascular tone, endothelial damage, and can contribute to blood–brain barrier breakdown (Pantoni, 2010; Wardlaw et al, 2013a; Wardlaw et al, 2013b).

While WMH have received significant attention in recent years due to their association with cognitive decline, understanding regarding the pathophysiology underlying their development and optimal treatment strategies remains limited, largely due to difficulty related to detection and accurate quantification of WMH. Research indicates that manual segmentation of WMH is not only time-consuming, but yields large intra- and inter-observer variabilities, ranging from 10 to 68% (Grimaud et al., 1996; Zijdenbos et al., 2002; Styner et al., 2008; Zhu et al, 2022). There is a

need for accurate and efficient WMH segmentation methods to decrease the burden on clinicians to identify lesion loads and volumes accurately. Two areas where more research is needed are accurate segmentation and volume quantification, as well as the performance of these methods on multi-center, multi-scanner datasets (Kuijf et al., 2019). Although various segmentation methods have been proposed, their performance is typically evaluated on single-center, single-scanner datasets, and there is a lack of studies comparing their performance in multi-center, multi-scanner datasets, which is an important knowledge gap (Kuijf et al., 2019; Valdés Hernández et al., 2013a; Valdés Hernández et al., 2013b). Achieving accurate and precise WMH segmentations can be challenging across MRI scanners of different vendors, field strengths, and scanning protocols, leading to variability in MRI acquisition and potential quantification bias (Kuijf et al., 2019; Valdés Hernández et al., 2013a; Valdés Hernández et al., 2013b).

3.2 Automated White Matter Hyperintensity Segmentation with HyperMapp3r

Manual segmentation is used as the benchmark for WMH analysis and is conducted to distinguish WMH from other tissue types and normal-appearing white matter. However, manual segmentation is time-consuming and requires extensive training. As a result, there is a need for automated methods for segmenting WMH. Klauschen et al. (2021) investigated the performance of several medical imaging networks and found that MR-based segmentation methods are highly sensitive to various factors such as acquisition protocols, scanners, noise-level, and image contrast. While many automated segmentation methods exist, studies conducted on the accuracy of WMH segmentations have produced varying results (Klauschen et al. 2021).

HyperMapp3r is a three-dimensional (3D) deep learning (U-Net model) method developed by Fooroshani et al. 2022 as a Bayesian network designed to automatically segment WMH from T1-weighted and FLAIR MRI scans and generate volume quantification of detected lesions (Fooroshani et al., 2022). The algorithm was initially trained on MRI data from 432 patients from varying diagnostic groups, including patients with small vessel ischemic disease and cerebrovascular diseases. HyperMapp3r was designed for handling variations in imaging acquisition protocols using augmentation of training data to learn permutations to noise level,

resolution, and contrast, making it insensitive to different MRI acquisition protocols and scanners and essentially, a highly robust segmentation tool.

3.3 Intensity Normalization Methods

Normalization methods in MRI scans increase the accuracy of segmentations by decreasing erroneous image variability, thereby standardizing the data, and increasing comparability between images. Intensity normalization reduces differences in image intensity across images and improves the consistency of the signal range, accounting for differences in scanner, protocol, and noise. Reducing intensity variations allows for more accurate comparisons and statistical analyses in group studies, thereby increasing the reliability of conclusions from MRI datasets. Additionally, it enables identification and investigation of subtle anatomical differences between images and patients, thus playing a crucial role in imaging research (Dai et al, 2008).

In a study by Reinhold et al. (2019), the authors presented several intensity normalization algorithms, including: Z-score, Fuzzy C-Means (FCM)-based, Kernel Density Estimate (KDE) based, and WhiteStripe. The Z-score method calculates the mean and standard deviation of intensities within the brain mask, then subtracts the mean and divides the image by the standard deviation. The FCM-based normalization uses fuzzy c-means to create a white matter (WM) mask. This mask is then used to normalize the entire image based on the mean intensity of the WM. The KDE-based normalization estimates the probability density function of intensities over the brain mask using kernel density estimation, identifies maxima in the WM, which are then used to normalize the image. Finally, WhiteStripe normalization performs a Z-score normalization based on the intensities of normal appearing white matter (NAWM). The highest peak in the histogram of the image represents the normal appearing white matter, and a segment around that peak is used to normalize (Reinholds et al. 2019). While these and various other intensity normalization methods have been proposed, it is unclear if these methods improve or even bias segmentation of WMH on MRI. In this study, we evaluated the effect of five intensity normalization methods in quantifying WMH segmented using HyperMapp3R to understand potential areas of bias and identify optimal methods that can enhance analysis of WMH in cases where its burden is unclear, such as in ARDS populations. As a secondary aim, we examined the performance of the novel WMH automated segmentation tool, HyperMapp3R in quantifying WMH lesions and volume.

3.4 Participant Characteristics

Anatomical MRI from 14 patients (average age 75.7, 66-84, ± 7.2) with ischemic stroke was utilized to test the normalization methods and validate HyperMapp3R. All participants were recruited from a single center, prospective study from the regional stroke centre for southwestern ontario located at London Health Sciences Center (LHSC), urgent transient ischemic attack (TIA) clinic at LHSC and Parkwood Institute who are admitted for a confirmed supratentorial hemispheric ischemic stroke with a diameter of the ischemic lesion of 15 mm or greater. Patients with a history of previous symptomatic stroke, presence of other neurological or psychiatric disease, such as dementia or mild cognitive impairment, prior to study entry, significant aphasia, evidence of other chronic co-morbid conditions or unstable acute systemic illnesses which could shorten the patient's survival or limit their ability to complete the study were excluded. All participants in the study underwent a whole-brain MRI scan on a 3T MRI scanner (Biograph mMR, Siemens Healthineers, Erlangen, Germany) equipped with 12-channel head array coils. White matter hyperintensity was assessed using a Sagittal T2-weighted sampling perfection with application optimized contrasts using different flip angle evolution (SPACE) fluid-attenuated inversion recovery (FLAIR) sequence and the following parameters: isotropic voxel resolution = 1.0 mm^3; repetition time = 4800 ms, echo time = 343 ms, inversion time = 1800 ms, and an acceleration factor = 2. Sagittal T1-weighted images were acquired for spatial normalization and group wise analysis using a three-dimensional (3D) magnetization-prepared rapid gradient-echo imaging sequence and the following parameters: isotropic voxel resolution = 1.0 mm^3; repetition time = 2300 ms, echo time = 2.98 ms, inversion time = 900 ms, acceleration factor = 2, and flip angle = 9°. All participants provided written informed consent. The study was approved by Western University Human Studies Research Ethics Board and conducted in accordance with the Declaration of Helsinki ethical standards.

Table 3.1: Patient Demographics and MRI Acquisition Parameters

	PSCI (n=14)
Variable	Outcome
Total MR Images/Sample Size (n)	14/14

Age *(years) Mean (range)* ± *SD*	75.7 (66-84) ± 7.2
Sex *(female) (%)*	37.5
WMH volume (mm^3, Manual Segmentation) Mean (*range*) ± *SD*	6538.1 (368.9-16660.7) ± *6078.1*

3.5 Methods

For each participant, the MRI data were preprocessed using the following steps (see Figure 3.2): 1) conversion from Digital Imaging and Communications in Medicine (DICOM) to Neuroimaging Informatics Technology Initiative (NIfTI) using SPM 12 (Maldjian et al. 2003), 2) separation of the brain from non-brain tissues in SPM12 by segmenting the brain into gray matter, white matter and cerebrospinal fluid, 3) the brain tissue segments were summed to generate a brain mask and crop the background such that all voxels outside the brain space were zero-valued, 4) the N4 bias correction algorithm implemented in 3D Slicer (Fodorov et al. 2012) was then used to correct native image intensity inhomogeneities from the spatial and time varying radiofrequency field. The image intensities of the preprocessed images were scaled using five intensity normalization methods: 1) WhiteStripe, 2) Z Score, 3) FCM, 4) KDE, and by 5) clipping the intensities (Reinhold et al. (2019), to generate five processed images for each participant. Manual segmentation was performed by two neuroradiologists, M.T.J. and P.O., to generate ground truth annotations using ITKSnap implemented in 3D Slicer (Fodorov et al. 2012; Yushkevich et al. 2006).

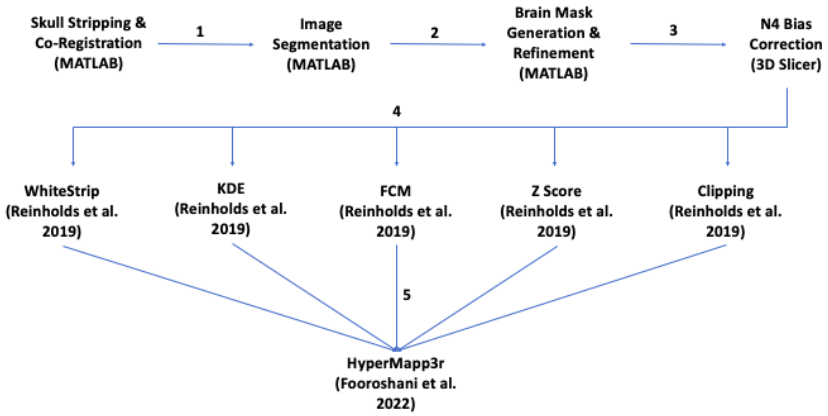


Figure 3.1: Schematic of MR image analysis pipeline

To quantify WMH lesion loads and volumes, the HyperMapp3r tool was used to segment WMH on preprocessed and intensity normalized images and generate lesion maps and volume. The lesion volume from manual segmentation was computed in Matlab (R2022a; MathWorks, Natick, USA). All WMH lesion volume was quantified in mm^3 and was normalized by total brain volume. Statistical analysis to compare automated WMH lesion maps and volumes to the manual segmentation reference was performed in Matlab using metrics for image similarity (Dice Similarity Index (DSC) and Jaccard Index (JI) and bias (percent relative volume difference (RVD%) = automated segmentation – manual segmentation/manual segmentation).

$$DSC(A,B)= 2(A \cap B)/(A+B)$$

$$JI(A,B) = |A \cap B|/|A \cup B|$$

Metrics reported as mean ± standard deviation (SD), unless otherwise noted. A DSC or JI of 1 indicates close similarities, while a near zero RVD% indicates no difference between measures. A within subject repeated measures ANOVA was also conducted to compare the WMH volumes from the five intensity normalization methods.

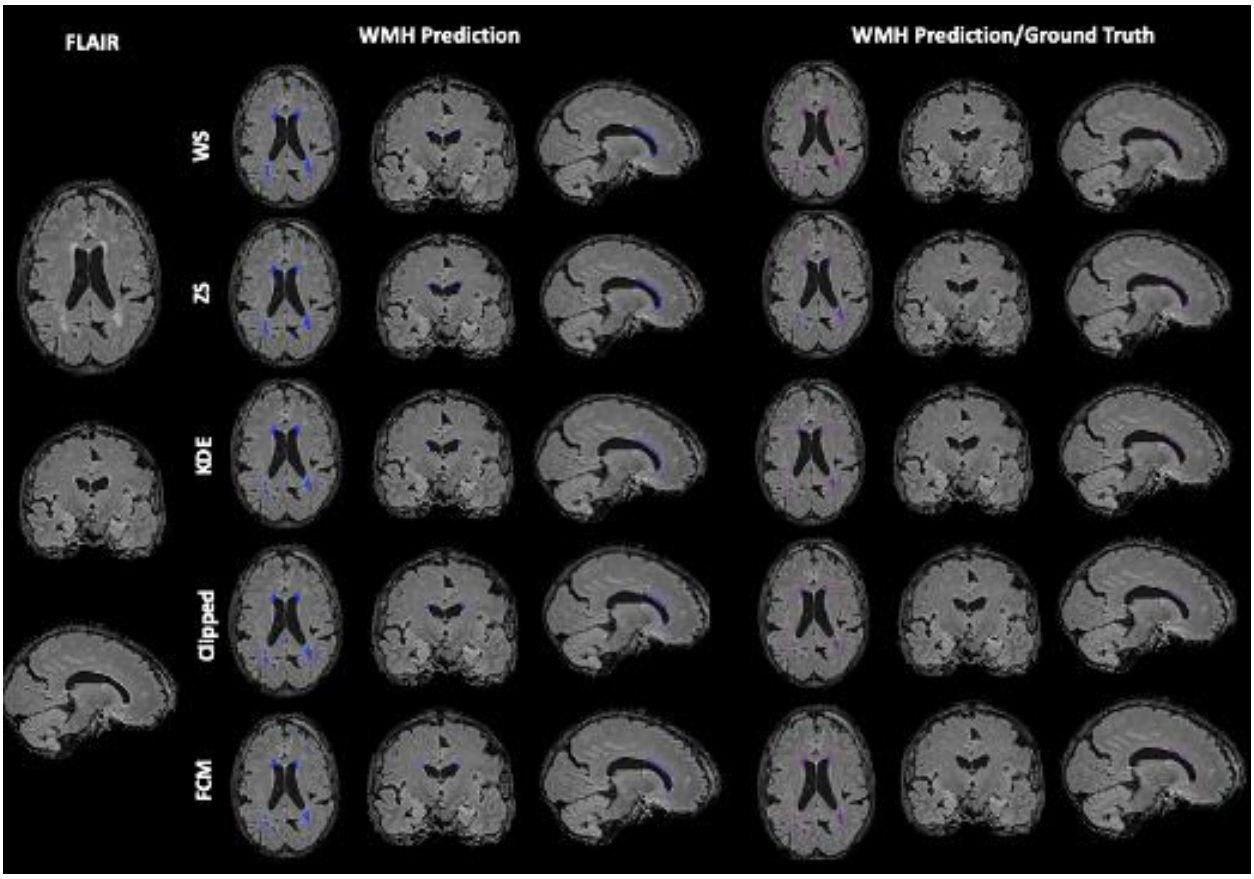


Figure 3.2: Patient 19 WMH segmentation on a FLAIR scan (axial, sagittal, and coronal views), showing HyperMapp3r's total WMH prediction (blue), and ground truth labels overlayed onto the model's predictions (red)

3.6 Results

The participant demographics and clinical profile are summarized in Table 3.1. Results of intensity normalization across the 14 MRI images are summarized in Table 3.2. WhiteStripe normalization achieved a DSC of 0.7 and JI 0.56. Z-score normalization, Fuzzy C-Means (FCM), Kernel Density Estimate (KDE) and clipped intensity normalization had the same moderate level of overlap and similarity (see Figures 3.2, 3.3).

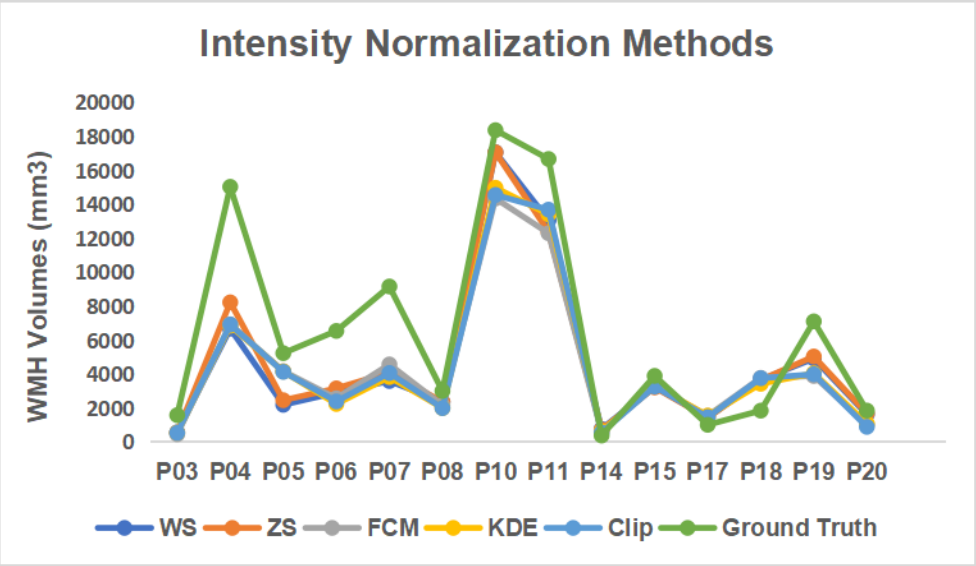


Figure 3.3: WMH volumes in mm^3 depicted across intensity normalization methods and patients

The mean WMH volumes calculated from HyperMapp3r automated segmentations for the five intensity normalization methods are outlined in Table 3.2 and an illustration of degree of overlap of WMH lesion maps between automated and the manual reference segmentations is shown in Figure 3.2 and 3.3. A within subject repeated measures ANOVA was conducted to compare the WMH volumes from the 5 intensity normalization methods and indicated there was not a statistically significant difference between the five intensity normalization methods ($p < 0.557513$; F-ratio value = 0.75777; between-treatments degrees of freedom = 4; within treatments degrees of freedom = 65).

Table 3.2: WMH outcomes and comparative analysis of automated and manual segmentations

	WhiteStripe	Z Score	KDE	FCM	Clipped
Variable	Outcome	Outcome	Outcome	Outcome	Outcome
Dice Similarity	0.7 ± *0.21*	0.67 ± *0.21*	0.62 ± *0.18*	0.61 ± *0.18*	0.61 ± *0.18*

Coefficient Mean, ± *SD*					
Jaccard Index Mean, ± *SD*	0.56 ± *0.25*	0.54 ± *0.23*	0.47 ± *0.19*	0.47 ± *0.19*	0.47 ± *0.18*
Relative volume difference Mean (%), ± *SD*	-0.11 ± *0.56*	-0.10 ± *0.52*	-0.16 ± *0.50*	-0.16 ± *0.52*	-0.18 ± *0.50*
WMH volume (mm^3, HyperMapp3r) Mean (*range*) ± *SD*	4569.3 (562.7-17055.6) ± *4790.5*	4705.9 (537.9-17054.1) ± *4753.4*	4421.0 (537.0-14965.6) ± *4474.3*	4394.2 (446.8-14336.7) ± *4182.9*	4430.8 (525.5-14542.7) ± *4457.2*

3.7 Discussion

In this study, we compared multiple intensity normalization methods designed to improve intensity signal bias common in MRI, particularly seen in clinical imaging studies.

While similar overlap measured as DSC were observed among normalization methods, the WhiteStripe method yielded relatively higher match between automated and manual segmentation. The DSC values calculated for MRI segmentations are known to vary, (Valdés-Hernández et al, 2013a; Valdés Hernández et al., 2013b) ranging from 0.71 to 0.99 using high quality data and machine learning algorithms (Bakx et al, 2023; Conte et al, 2021; Malla et al, 2019). A systematic review of available automated segmentation performance indicated average DSC values ranging from 0.54 to 0.91, the higher values being obtained using data with higher spatial resolution (Balakrishnan et al. 2021). While methods differ, our results indicate normalization methods may

not meaningfully alter volume estimates, suggesting variations in reported DSC values may instead relate to imaging artifacts and noise, with lower image quality generally reducing DSC values. The standard deviations across each method and the ground truth manual segmentations indicate a high degree of data variability between scans, which may suggest variability amongst the patient data and differing presentations of pathologies. In the case of aberrant structural lesions, it may be necessary to control for resultant bias when implementing normalization methods. WhiteStripe could be considered for cases with the presence of other anatomical lesions, such as stroke, to minimize the bias of these lesions which may confound this method. Other novel normalization methods such as Ravel (Fortin et al. 2016), have been reported to improve WhiteStripe by estimating the mitigating data variations using an additive model and information such as scanner variability and clinical covariates, including individual cerebrospinal fluid image intensities to model and correct for potential sources of inter-subject variability (Fortin et al. 2016). . This method could be considered for longitudinal and multi-center studies, especially if the influence from scanner differences, pathologies, and other physiological confounders could significantly bias results.

The significance of estimating accurate WMH load in stroke populations are well understood, given that the risk for stroke recurrence increases with increasing WMH load, both in ischemic and more so in hemorrhagic stroke (Ryu et al. 2019). Estimates of WMH load and volume have been linked to slower cognitive and psychomotor processing speed, indicating significant impact on quality of life and potentially accelerating progression of cognitive decline (Guo et al, 2022; Yang et al, 2007). Decreased white matter integrity has also been linked to executive control dysfunction in COVID-19, manifesting as slow speed of processing in a recent study of 38 COVID-19 patients hospitalized for complications of SARS-CoV-2 infection. In the study, 42.1% of COVID-19 patients experienced processing speed deficits and 26.3% showing delayed verbal recall deficits (Ferruci et al. 2021), which is thought to relate to changes in white matter integrity of the brain. Taken together, the burden of WMH in vulnerable patient groups places emphasis on accurate quantification to guide improved and adaptive healthcare strategies. Post-acute sequelae characterizing COVID-19 ARDS will likely have a profound impact not only on patients' quality of life, but on public health systems globally, requiring an immediate and coordinated response. Given the stress on the healthcare system by the aging population and the consequences of

neurological impact in a post-pandemic world, a better understanding of WMH pathogenesis, accurate segmentation and quantification of lesion loads and volumes, and increased efficiency quantifying WMH will be essential to support the growing elderly population, particularly in the post-pandemic era. Utilizing automatic segmentation methods to enable timely and efficient analysis of WMH burden and lesion volumes will be essential for gaining a better understanding of the extent of white matter injury. For populations where white matter pathologies are unclear, such as COVID-19, careful consideration should still be paid on the choice of intensity normalization methods, particularly for analysis of MRI data from clinical scans, where image quality may be reduced due to acquisition on clinical strength (1.5T) scanner and protocols. Although the findings of this study highlight the importance of intensity normalization methods in WMH analysis, there are methodological drawbacks that should be considered. First, the results were limited by a small sample size, which may decrease representativeness of the patient group and restricts the sensitivity and accuracy in detecting differences between intensity normalization methods. Second and most important, the datasets utilized were acquired from post-stroke patients from a single scanner and single site, further limiting generalization of findings to datasets acquired from other MRI scanners, sites, or patient groups. WMH present differently across pathologies due to differing pathophysiological factors, brain injury types, patterns, and location of lesions. This can affect the performance of normalization methods, which were not examined in this study . Future studies in larger cohort of mixed pathologies (COVID-19 ARDS small vessel disease, stroke, multiple sclerosis, etc.) and including other types of normalization techniques, is required to confirm the influence of intensity normalization on automated estimation of WMH lesion volumes.

3.8 References

1. Bakx, N., van der Sangen, M., Theuws, J., Bluemink, H., Hurkmans, C. (2023). Comparison of the output of a deep learning segmentation model for locoregional breast cancer radiotherapy trained on 2 different datasets. *tipsRO*, 26, 100209.
2. Balakrishan, R., Valdes Hernandez, M.C., Farrall, A.J. (2021). Automatic segmentation of white matter hyperintensities from brain magnetic resonance images in the era of deep learning and big data – A systematic review. *Comput Med Imaging Graphics,* 88, 101867.
3. Conte, G.M., Weston, A.D., Vogelsang, D.C., Philbrick, K.A., Cai, J.C., Barbera, M., Sanvito, F., Lachance, D.H., Jenkins, R.B., Tobin, W.O., Echecl-Passow, J.E., Erickson, B.J. (2021). Generative Adversarial Networks to Synthesize Missing T1 and FLAIR MRI Sequences for Use in a Multisequence Brain Tumor Segmentation Model. *Radiology,* 299, 313-323.
4. Dai, W., Carmichael, O.T., Lopez, O.L., Becker, J.T., Kuller, L.H., Gach, M. (2008). Effects of image normalization on the statistical analysis of perfusion MRI in elderly brains. *J Mag Res Imagin*g, 28(6), 1351-1360.
5. Ferrucci, R., Dini, M., Groppo, E., Rosci, C., Reitano, M. R., Bai, F., Poletti, B., Brugnera, A., Silani, V., D'Arminio Monforte, A., & Priori, A. (2021). Long-Lasting Cognitive Abnormalities after COVID-19. *Brain Sci,* 11(2), 235.
6. Fodorov A., Beichel R., Kalpathy-Cramer J., Finet J., Fillion-Robin J-C., Pujol S., Bauer C., Jennings D., Fennessy F.M., Sonka M., Buatti J., Aylward S.R., Miller J.V., Pieper S., Kikinis R. (2012). 3D Slicer as an Image Computing Platform for the Quantitative Imaging Network. *Magn Reson Imaging*, 30(9), 1323-41.
7. Forooshani, P., Biparva, M., Ntiri, E. E., Ramirez, J., Boone, L., Holmes, M. F., Adamo, S., Gao, F., Ozzoude, M., Scott, C. J. M., Dowlatshahi, D., Lawrence-Dewar, J. M., Kwan, D., Lang, A. E., Marcotte, K., Leonard, C., Rochon, E., Heyn, C., Bartha, R., Strother, S., Tardif, J.-C., Symons, S., Masellis, M., Swartz, R. H., Moody, A., Black, S. E., & Goubran, M. (2022). Deep Bayesian networks for uncertainty estimation and adversarial resistance of white matter hyperintensity segmentation. *NeuroImage,* 245, 2089-2108.

8. Fortin, J.P., Sweeney, E.M., Muschelli, J., Crainiceanu, C.M., Shinohara, R.T. (2016). Alzheimer's Disease Neuroimaging Initiative. Removing inter-subject technical variability in magnetic resonance imaging studies. Neuroimage, 132, 198-212.
9. Garde, E., Mortensen, E.L., Krabbe, K., Rostrup, E., Larsson, H.B. (2000). Relation between age-related decline in intelligence and cerebral white-matter hyperintensities in healthy octogenarians: a longitudinal study. *Lancet*, 356, 628-634.
10. Grimaud, J., Lai, M., Thorpe, J., Adeleine, P., Wang, L., Barker, G.J., Plummer, D.L., Tofts, P.S., McDonald, W.I., Miller, D.H. (1996). Quantification of MRI lesion load in multiple sclerosis: A comparison of three computer-assisted techniques. *Mag Res Imaging,* 14 (5): 495-505.
11. Guo W, Shi J. (2022). White matter hyperintensities volume and cognition: A meta-analysis. *Front Aging Neurosci*, 1;14:949763.
12. Hirose, T., Totsune, K., Nakashige, Y., Metoki, H., Kikuya, M., Ohkubo, T., Hara, A., Satoh, M., Inoue, R., Azayama, K., Kondo, T., Kamide, K., Katsuya, T., Ogihara, T., Iumi, S., Rakugi, H., Takahashi, K., Imai, Y. (2011). Influence of adrenomedullin 2/intermedin gene polymorphism on blood pressure, renal function and silent cerebrovascular lesions in Japanese: the Ohasama study. *Hypertens Res* 34, 1327–1332
13. Jochems, A. C. C., Arteaga, C., Chappell, F., Ritakari, T., Hooley, M., Doubal, F., Muñoz Maniega, S., & Wardlaw, J. M. (2022). Longitudinal Changes of White Matter Hyperintensities in Sporadic Small Vessel Disease: A Systematic Review and Meta-analysis. *Neurology*, 99(22), e2454–e2463.
14. Jovicich, J., Czanner, S., Greve, D., Haley, E., van der Kouwe, A., Gollub, R., Kennedy, D. (2006). Reliability in multi-site structural MRI studies: effects of gradient non-linearity correction on phantom and human data. *NeuroImage,* 30(2), 436-443.
15. Klauschen F, Goldman A, Barra V, Meyer-Lindenberg A, Lundervold A. (2009). Evaluation of automated brain MR image segmentation and volumetry methods. *Hum Brain Mapp,* 30(4):1310-27.
16. Kloppel, S., Abdulkadir, A., Clifford, J.R., Koutsouleris, N., Mourao-Miranda, J., Vemuri, P. (2012). Diagnostic neuroimaging across diseases. *NeuroImage,* 61(2), 457-463

17. Kuijf, H. J., Biesbroek, J. M., de Bresser, J., Heinen, R., Andermatt, S., Bento, M., Berseth, M., Brett, M., Carle, A., Chalela, J., Dohmen, C., Emsell, L., Flottmann, F., van der Flier, W. M., Gracien, R. M., Ghafoorian, M., Goebel, R., Håberg, A. K., Habert, M. O., de Leeuw, F. E. (2019). Standardized assessment of automatic segmentation of white matter hyperintensities; results of the WMH segmentation challenge. *IEEE Trans Med Imaging,* 38(11), 2556-2568.
18. Lesjak, Ž., Spiclin, Z., Likar, B., Pernuš, F. (2014). Validation and comparison of intensity based methods for change detection in serial brain images. *Proc. SPIE 9037, Medical Imaging 2014: Image Perception, Observer Performance, and Technology Assessment,* 90371C.
19. Lin, Q., Huang, W.Q., Ma, Q.L., Lu, C.X., Tong, S.J., Ye, J.H., Lin, H.N., Gu, L., Yi, K.H., Cai, L.L., Tzeng, C.M. (2017). Incidence and risk factors of leukoaraiosis from 4683 hospitalized patients: A cross-sectional study. *Medicine*, 96(39), e7682.
20. Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH. (2003). An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *Neuroimage,* 19(3), 1233–9.
21. Malla, C.U.P, Valdés Hernández, M.D.C., Rachmadi, M.F., Komura, T. (2019). Evaluation of Enhanced Learning Techniques for Segmenting Ischaemic Stroke Lesions in Brain Magnetic Resonance Perfusion Images Using a Convolutional Neural Network Scheme. *Front Neuroinform*, 29, 13-33.
22. Marini S, Georgakis MK, Chung J, Henry JQA, Dichgans M, Rosand J, Malik R, Anderson CD. (2020). Genetic overlap and causal inferences between kidney function and cerebrovascular disease. *Neurology,*16;94(24): e2581-e2591.
23. MATLAB. (2022). Version R2022a. Natick, Massachusetts: The MathWorks Inc.
24. Pantoni, L. (2010). Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. *Lancet Neurol*, 9(7), 689-701.
25. Persyn, E., Hanscombe, K.B., Howson, J.M.M. Lewis, C.M., Traylor, M. Markus, H.S. (2020). Genome-wide association study of MRI markers of cerebral small vessel disease in 42,310 participants. *Nat Commun* 11, 2175.
26. Prins, N. D. & Scheltens, P. (2015). White matter hyperintensities, cognitive impairment and dementia: An update. *Nat Rev Neurol*, 11(3), 157–165.

27. Reinhold, J.C., Dewey, B.E., Carass, A., Prince, J.L. (2019). Evaluating the Impact of Intensity Normalization on MR Image Synthesis. Proc. *SPIE 10949, Medical Imaging 2019: Image Processing*, 109493H.
28. Rensma, S. P., van Sloten, T. T., Launer, L. J., & Stehouwer, C. D. A. (2018). Cerebral small vessel disease and risk of incident stroke, dementia and depression, and all-cause mortality: A systematic review and meta-analysis. *Neurosci biobehavioral rev*, 90, 164–173.
29. Ryu, W.S., Schellingerhout, D., Hong, K.S., Jeong, S.W., Jang, M.U., Park, MS.., Choi, K.H., Kim, J.T., Kim, B.J., Lee, J., Cha, J.K., Kim, D.H., Nah, H.W., Lee, S.J., Kim, J.G., Cho, Y.J., Lee, B.C., Yu, K.H., Oh, M.S., Park, J.M., Kang, K., Lee, K.B., Park, T.H., Park, S.S., Lee, J., Bae, H.J., Kim, D.E. (2019). White matter hyperintensity load on stroke recurrence and mortality at 1 year after ischemic stroke. Neurology, 93(6), e578-e589.
30. Schmidt, P., Gaser, C., Arsic, M., Buck, D., Förschler, A., Berthele, A., Zimmer, C. (2012). An automated tool for detection of FLAIR-hyperintense white-matter lesions in multiple sclerosis. *NeuroImage,* 59(4), 3774-3783.
31. Shao, I.Y., Power, M.C., Mosley, T., Clifford, J., Gottesman, R.F., Chen, L.Y., Norby, F.L.M Soliman, E.Z., Alonso, A. (2019). Association of Atrial Fibrillation with White Matter Disease. *Stroke,* 50(4), 989-991.
32. Shinohara, R. T., Sweeney, E. M., Goldsmith, J., Shiee, N., Mateen, F. J., Calabresi, P. A., Jarso, S., Pham, D. L., Reich, D. S., Crainiceanu, C. M., Australian Imaging Biomarkers Lifestyle Flagship Study of Ageing, Alzheimer's Disease Neuroimaging Initiative, (2014). Statistical normalization techniques for magnetic resonance imaging. *NeuroImage: Clinical,* 6, 9-19.
33. Smith, E. E., Saposnik, G., Biessels, G. J., Doubal, F. N., Fornage, M., Gorelick, P. B., Greenberg, S. M., Higashida, R. T., Kasner, S. E., Seshadri, S., & American Heart Association Stroke Council; Council on Cardiovascular Radiology and Intervention; Council on Functional Genomics and Translational Biology; and Council on Hypertension (2017). Prevention of Stroke in Patients With Silent Cerebrovascular Disease: A Scientific Statement for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke*, 48(2), e44–e71.

34. Styner, M., Brechbühler, C., Székely, G., & Gerig, G. (2000). Parametric estimate of intensity inhomogeneities applied to MRI. *IEEE Trans on Med Imaging*, 19(3), 153-165.
35. Valdes Hernández, M.C., Morris, Z., Dickie, D.A., Royle, N.A., Maniega, S.M., Aribisala, B.S.. Bastin, M.E., Deary, I.J., Wardlaw, J.M. (2013a). Close Correlation between Quantitative and Qualitative Assessments of White Matter Lesions. *Neuroepidemiology,* 40 (1) 13-22.
36. Valdés-Hernández, M.D.C., Piper, R.J., Wang, X., Deary, I.J., Wardlaw, J.M. (2013b). Towards the Automatic Computational Assessment of Enlarged Perivascular Spaces on Brain Magnetic Resonance Images: A Systematic Review. *J Magn Res Imaging*, 40(1), 13-22.
37. van Leijsen, E.M.C., de Leeuw, F., Tuladhar, A. (2017). Disease progression and regression in sporadic small vessel disease–insights from neuroimaging. *Clin Sci*, 131 (12), 1191–1206.
38. Wardlaw, J. M., Smith, C., & Dichgans, M. (2013a). Mechanisms of sporadic cerebral small vessel disease: insights from neuroimaging. *Lancet. Neurol*, *12*(5), 483–497.
39. Wardlaw, J. M. et al. (2013b). Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol*. 12(8), 822–838.
40. Wardlaw, J. M., Valdes Hernandez, M. C., Munoz-Maniega, S. (2015). What are white matter hyperintensities made of? Relevance to vascular cognitive impairment. J. *Am. Heart Assoc.* 4(6), 001140.
41. Yang, Q., Huang, X., Hong, N., & Yu, X. (2007). White matter microstructural abnormalities in late-life depression. *International Psychogeriatrics*, 19(4), 757-766.
42. Ylikoski A, Erkinjuntti T, Raininko R, Sarna S, Sulkava R, Tilvis R. (1995). White matter hyperintensities on MRI in the neurologically non diseased elderly. Analysis of cohorts of consecutive subjects aged 55 to 85 years living at home. *Stroke*, 26, 1171-1177.
43. Yushkevich, P., Piven, J., Cody, H., Hazlett, R., Smith, G., Ho, S., Gee, J., Gerig., G. (2006). User-guided 3D active contour segmentation of anatomical structures: Significantly improved efficiency and reliability. *Neuroimage,* 131(3), 1116-28.

44. Zhu, W., Huang, H., Zhou, Y., Shi, F., Shen, H., Chen, R., Hua, R., Wang ,W., Xu, S., Luo, X. (2022) Automatic segmentation of white matter hyperintensities in routine clinical brain MRI by 2D VB-Net: A large-scale study. *Front Aging Neurosci.* 29;14:915009.
45. Zijdenbos, A. P., Dawant, B. M., Margolin, R. A., & Palmer, A. C. (1994). Morphometric analysis of white matter lesions in MR images: method and validation. *IEEE Trans Med Imaging,* 13(4), 716-724.

Chapter 4

4.1 Conclusions

COVID-19 infection leading to acute respiratory distress syndrome (ARDS) has been associated with impaired brain function and is implicated in damage to the vasculature of the brain. Research indicates inflammatory-induced damage, hypoxemia due to direct and indirect lung damage, and endothelial dysfunction may contribute to the prevalence of brain injuries in COVID-19 and ARDS. In Chapter 2, a systematic review and meta-analysis was conducted to better understand brain outcomes in these populations. The results suggests that the combination of ARDS and COVID-19 increases the risk of developing ICH relative to ARDS, and that there may be higher prevalence of impact to the white matter of the brain in COVID-19 ARDS, commonly manifesting as WMH. Given the findings of the review, the impact of intensity normalization methods on the performance of novel deep learning-based methods for WMH segmentation was explored in Chapter 3 and the methods assessed were found to yield similar segmentation results.

The increased risk of ICH in COVID-19 ARDS poses a particular area of concern within this patient group. ICH following COVID-19 infection has been associated with a longer ICU stay, more time mechanically ventilated and a higher risk for mortality (Daly et al., 2021; Dhamoon et al., 2021). Daly et al. 2021 indicated the rate of ICH as being between 0.1% and 3.3% of hospitalized COVID-19 patients, with increased risk for patients >80 years old. ICH in COVID-19 is linked to increased morbidity and higher prevalence of vasopressor support across differing types of ICH, including SAH, SDH/EDH, and IPH (Daly et al. 2021). Several mechanisms have been proposed to explain the neurological impact contributed by COVID-19 infection, including direct neurotropism, dysregulation of the renin-angiotensin system (RAS) system due to ACE-2 binding, coagulopathy due to endothelial damage, release of inflammatory factors activating macrophages, microglia and astrocytes, systemic hypoxemia due to breakdown of pulmonary surfactant, and endothelial dysfunction (Ackermann et al. 2020; Wang et al., 2023). White matter may be at greater risk for inflammatory-induced damage due to higher concentrations of cytokine and glutamate receptors along myelinated tracts, potentially conferring greater sensitivity to release of inflammatory factors (Lin et al., 2020). Subsequent endothelial dysfunction and coagulopathy in COVID-19 due to extensive tropism of SARS-CoV-2 could contribute to the

higher reported incidence of WMH and ischemic stroke in COVID-19 ARDS patients. While researchers speculate regarding a potential direct effect of SARS-CoV-2 infection and neurological impact, current data indicates COVID-19 ARDS patients present with higher incidence of pre-existing risk factors, particularly diabetes, obesity, and immunodeficiencies, and are likelier to be affected by socioeconomic factors (Bain et al., 2020; Brault et al., 2020; Wang et al., 2022). It is therefore difficult to ascertain the likelihood of a causal link between COVID-19 infection and observed patterns of brain injuries, additionally due to the complex course of treatments and high prevalence of mechanical ventilation in COVID-19 ARDS patients, which also poses risk for adverse health outcomes including brain damage, bleeding, and vascular injury (Combes et al., 2018; Matthay et al., 2019).

Taken together, the systematic review presented in Chapter 2 indicates there is an increased risk for developing ICH in COVID-19 ARDS relative to non-COVID-19 ARDS, and COVID-19 ARDS patients may present with a higher prevalence of white matter injury. The burden of COVID-19 is substantial and distinct from ARDS as indicated by increased risk of developing ICH and other brain injuries of other causes. This places emphasis on the need for sensitive imaging biomarkers to identify ARDS-related brain injuries, quantify their impact and understand their underlying mechanisms to develop adaptive healthcare strategies to support survivors in the post-pandemic era. Several methods have been proposed to automatically quantify WMH including emerging techniques based on deep learning. However, the influence of image preprocessing steps that could alter the image intensities and bias automated segmentation approaches have been underexplored and not well tested. In Chapter 3, we illustrated the effect of intensity normalization methods on deep learning segmentation accuracy, while preliminary, suggests careful consideration of normalization approach may be required for WMH analysis in ARDS populations including those with COVID-19.

While several important and novel findings were achieved in this work, the results presented were impacted by several methodological limitations. Systematic review relies on available retrospective data and the quality of the data. The sparse description and demographic information in published studies documenting clinical and imaging outcomes in critical illness patients, comprehensive list of comorbidities and medications of the cohort, limits the understanding of

brain findings, which is further complicated in the case of infectious disease. The brain findings could also be limited by the sheer feasibility in conducting imaging in very sick patients, which will result in imaging being conducted in the more compliant patients, especially those who have MRI contraindications, due in part to severity of their illness (i.e., no contrast administration from renal function impairments, etc.). The difficulty in recruiting and mitigating attrition in this patient group due to the fragility and health complications inherent to patients with ARDS limits consistency and generalizability of results. In addition, the patients were frequently recruited selectively rather than being subject to randomization procedures which increases variability in available data. There was also a difference in reporting of clinical and brain imaging findings between non-COVID-19 ARDS and COVID-19 ARDS publications, such that the latter included more detailed and comprehensive neuroimaging results. There was also a difference in the neuroimaging modality used between the two groups, as evidence by the Chi-Squared test included in the results of Chapter 2 which indicated that there was a statistically significant preference for the use of MRI in the COVID-19 ARDS studies, whereas there was no statistically significant preference for the use of MRI or CT in the non-COVID-19 ARDS studies. This may contribute to underreporting in ARDS and potentially increasing the likelihood of underestimation of neurological involvement in these patients. For the findings described in Chapter 3, the relatively small sample sized data acquired from a single disease group in a single site study, limits the ability to effectively gauge the impact of normalization techniques on automated WMH segmentation approaches.

Finally, it is important to highlight that COVID-19 ARDS patients as a population receive multiple forms of treatments and medications and typically present with higher prevalence of comorbidities and risk factors independently associated with brain injury, potentially conferring heightened vulnerability to brain damage, and presenting an important confounding factor (Combes et al., 2018; Matthay et al., 2019).

Future studies should seek to establish neuroimaging findings in COVID-19 ARDS populations with larger sample sizes and with consideration for baseline characteristics including comorbidities and treatments and aim to document longitudinal outcomes following brain injury to investigate the likelihood and prevalence of long-term damage and potential functional impairments. Ideally,

these studies should be designed to quantitatively estimate WMH and its role on long-term brain health post-ARDS, especially post-COVID-19 ARDS. This will require careful consideration of image processing including choice of intensity normalization techniques for automated WMH segmentation and lesion volume estimation. A study evaluating the varying performance of intensity normalization methods is still needed in a larger cohort of mixed pathologies (COVID-19 ARDS small vessel disease, stroke, multiple sclerosis, etc.), and in brain images from longitudinal and multi-center studies to confirm the influence of intensity normalization on automated estimation of WMH lesion volumes. Current efforts are underway to explore additional intensity normalization approaches using the methodology outlined in Chapter 3 including methods such as Ravel (Fortin et al. 2016), on the Neuro-Save ICU data to determine the optimal approach for WMH analysis in COVID-19 ARDS patients enrolled in the study. As we emerge from the COVID-19 pandemic, the consequences of associated impairments will become increasingly important to understand. Given a potential difference COVID-19 ARDS and non-COVID-19 ARDS, our findings highlight the need for the attention towards the use of brain imaging analysis techniques and to white matter injury in considerations of public health assessment.

4.2 References

1. Ackermann, M., Verleden, S.E., Kuehnel, M., Haverich, A., Welte, T., Laenger, F., Vanstapel, A., Werlein, C., Stark, H., Tzankov, A., Li, W.W., Li, V.W., Mentzer, S.J., Jonigk, D. (2020). Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. *N Engl J Med*, 9;383(2), 120-128.
2. Bain, A., Yang, W., Shah, F. (2021). COVID-19 versus Acute Respiratory Distress Syndrome: Comparison of Demographics, Physiologic Parameters, Inflammatory Biomarkers, and Clinical Outcomes. *Ann Am Thorac Soc,* 18(7), 1202–1210.
3. Brault, C., Zerbib, Y., Kontar, L., Fouquet, U., Carpentier, M., Metzelard, M., Soupison, T., De Cagny, B., Maizel, J., Slama, M. (2020). COVID-19- versus non-COVID-19-related acute respiratory distress syndrome: differences and similarities. *Am J Respir Crit Care Med*, 202, 1301–1304.
4. Combes, A., Hajage, D., Capellier, G., Demoule, A., Lavoué, S., Guervilly, C., Da Silva, D., Zafrani, L., Tirot, P., Veber, B., Maury, E., Levy, B. (2018). Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. *New Eng J Med,* 378, 1965-1975.
5. Dhamoon, M.S., Thaler, A., Gururangan, K., Kohli, A., Sisniega, D., Wheelwright, D., Mensching, C., Fifi, J., Fara, M.G., Jette, J., Cohen, E., Dave, P., DiRisio, A., Goldstein, J., Loebel, E., Mayman, N., Sharma, A., Thomas, D., Vega Perez, R., Weingarten, M., Wen, H., Tuhrim, S., Stein, L. (2021). Acute Cerebrovascular Events With COVID-19 Infection. *Stroke,* 52(1), 48-56.
6. Daly, S.R., Nguyen, A.V., Zhang, Y., Feng, D., Huang, J.H. (2021). The relationship between COVID-19 infection and intracranial hemorrhage: A systematic review. *Brain Hemorrhages,* 2(4), 141-150.
7. Fortin, J.P., Sweeney, E.M., Muschelli, J., Crainiceanu, C.M., Shinohara, R.T. (2016). Alzheimer's Disease Neuroimaging Initiative. Removing inter-subject technical variability in magnetic resonance imaging studies. Neuroimage, 132, 198-212.
8. Lin J, Lawson EC, Verma S, Peterson RB, Sidhu R. (2020). Cytotoxic Lesion of the Corpus Callosum in an Adolescent with Multisystem Inflammatory Syndrome and SARS-CoV-2 Infection. *AJNR Am J Neuroradiol*, 41(11), 2017-2019.

9. Matthay, M. A., Zemans, R. L., Zimmerman, G. A., Arabi, Y. M., Beitler, J. R., Mercat, A., Herridge, M., Randolph, A.G., Calfee, C.S. (2019). Acute respiratory distress syndrome. *Nat Rev Dis Prim,* 5, 18.
10. Wang, L., Davis, P.B., Volkow, N.D., Berger, N.A., Kaelber, D.C., Zu, Rong. (2022). Association of COVID-19 with New-Onset Alzheimer's Disease. *J Alzheimers Dis*, 89, 411-414.
11. Wang M, Yu F, Chang W, Zhang Y, Zhang L, Li P. (2023). Inflammasomes: a rising star on the horizon of COVID-19 pathophysiology. *Front Immunol*, 12(14), 1185233.

Appendices

Appendix A: Comprehensive search strategies

Table A1. Comprehensive search strategy for Embase

Database	Ovid EMBASE ALL
1	adult respiratory distress syndrome/ (51879)
2	(respirator$ adj2 distress$ adj2 syndrom$).tw,kw. (46195)
3	ARDS.tw,kw. (29669)
4	((acute$ or adult$ or severe$) adj3 (respirator$ adj3 distress$)).tw,kw. (38964)
5	(lung$ adj2 shock$).tw,kw. (1037)
6	(((post traumatic$ or posttraumatic$) adj3 (respirator$ or lung$)) and failure$).tw,kw. (108)
7	((post traumatic$ or posttraumatic$) adj3 pulmonar$ adj3 insufficienc$).tw,kw. (107)
8	exp *respiratory failure/ (30818)
9	(respirat$ adj3 (distress$ or failure$ or insufficien$ or paralysis$ or deficienc$ or disturbanc$ or depression)).tw,kw. (169639)
10	(acute$ and ((respirat$ adj2 insufficienc$) or (respirat$ adj2 failure$))).tw,kw. (34532)
11	*acute lung injury/ (8510)
12	(acute$ and (lung$ adj2 injur$)).tw,kw. (30226)
13	((lung$ or pulmonary$) adj3 (failure$ or insufficien$)).tw,kw. (18906)
14	or/1-13 [Seach Concept: adult respiratory distress syndrome MEDLINE] (240598)
15	(critical$ adj2 ill$).tw,kw. or *Critical Illness/ or critically ill patient/ or critically$.tw,kw. (232892)
16	intensive care/ or intensive care unit/ or (ICU or ICUs or ((intensive care$ or intensive therapy$ or intensive treatment$ or high dependency$ or (coronary$ adj2 care$) or critical$ care) adj2 unit$) or MICU or CICU or CVICU or CCU$1 or SICU or POCCU$1 or HDU?ITU or ITU$1 or HDU$1).mp. or (critical$ and (intensive adj care)).mp. or (intensiv$ therap$ or intensiv$ treat$).tw,kw. (505388)
17	exp artificial ventilation/ or ((ventilat$ adj2 (artificial$ or mechanical$)) or (respirat$ adj2 (artificial$ or assisted$ or mechanical$)) or (respirat$ adj2 failure$)).tw. (306503)

18	(ventilat$ adj2 (weaning or support$)).tw,kw. or ((positive adj3 pressure adj5 (ventilat$ or respir$)) or (PPV and (pressure or ventilat$))).tw. or (ventilat$ adj3 patient$).ti. or (ventilat$ and patient$).ab. /freq=3 (83451)
19	or/15-18 (886438)
20	14 and 19 (122988)
21	exp *neurologic examination/ or exp *neuroradiology/ or *neuronavigation/ (177265)
22	exp neuroimaging/ or (neuronavigat$ or neuro-navigat$ or neuroimag$ or neuro-imag$ or (neurolog$ adj3 (evaluat$ or assess$ or examin$)) or neuroradiogr$ or neuro-radiogr$).tw,kw. (266103)
23	"cortical thickness (brain)"/ or (thickness$ adj3 (cortical$ or brain or cerebral$ or cortex$)).tw,kw. (18760)
24	exp *computer assisted emission tomography/ or "Fluorodeoxyglucose F 18"/ or (f-18$ or f18$ or fluorine-18$ or 18f$ or 18-f$ or fluorodeoxyglucose$ or FDG$).tw,kw. (218813)
25	((PET$ or "P.E.T.") and (scan$ or imag$3 pr stag$ or F-18$ or f18$ or 18f$ or 18-f$ or fluorine-18$ or fluorodeoxyglucose$ or FDG$)).tw,kw. (130976)
26	(magnetic resonance imag$ or imaging$ or mri$ or fMRI$ or (fluid?attenuat$ inversion$ recover$ or FLAIR)).tw,kw. (1648161)
27	((cat or ct$) adj2 (scan$ or x?ray or examination or imag$ or compute$ or electron or beam$ or diagnos$)).tw,kw. (379708)
28	PET?CT.tw,kw. (9272)
29	or/21-28 [imaging filter_EMBASE] (2246739)
30	(cerebr$ or intra?cerebral$ or cortical$ or subcortical$ or sub-cortical$ or cortex or brain$ or neurolog$).tw,kw. or exp *brain disease/ or (brain$ adj5 (disease$ or disorder$)).tw,kw. (3618760)
31	(hyperintens* or ((white$ or white?gr?y$) adj3 matter$) or lepto?mening$ or meningitis$ or meningo?encephalitis or demyelination or dysmyelination or myelitis or leukoencephalopath$ or encephal* or ADEM).tw,kw. (434019)
32	or/30-31 (3763324)
33	29 and 32 (768941)
34	20 and 33 [Q 1 set_Non-COVID-ARDS cohorts _Neuroimaging_Brain Injury] (3439)
35	(((exp Coronavirus/ or exp Coronavirus Infections/ or (coronavirus* or corona virus* or OC43 or NL63 or 229E or HKU1 or HCoV* or ncov* or covid* or sars-cov* or sarscov* or Sars-coronavirus* or Severe Acute Respiratory Syndrome Coronavirus* or D614G).mp.) not (SARS or SARS-CoV or MERS or MERS-CoV or Middle East respiratory syndrome or camel* or dromedar* or equine or coronary or coronal or covidence* or covidien or influenza virus or HIV or bovine or calves or TGEV or feline or

	porcine or BCoV or PED or PEDV or PDCoV or FIPV or FCoV or SADS-CoV or canine or CCov or zoonotic or avian influenza or H1N1 or H5N1 or H5N6 or IBV or murine corona*).mp.) or (((pneumonia or covid* or coronavirus* or corona virus* or ncov* or 2019-ncov or sars*).mp. or exp pneumonia/) and Wuhan.mp.) or (coronavirus disease 2019 or 2019-ncov or ncov19 or ncov-19 or 2019-novel CoV or severe acute respiratory syndrome coronavirus 2 or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or coronavirus-19 or covid19 or covid-19 or covid 2019 or ((novel or new or nouveau) adj2 (CoV or nCoV or covid or coronavirus* or corona virus or Pandemi*2)) or ((covid or covid19 or covid-19) and pandemic*2) or (coronavirus* and pneumonia)).mp. or (coronavirus disease 2019 or severe acute respiratory syndrome coronavirus 2).sh,dj.) and 20191201:20301231.(dc). (361582)
36	14 and 33 and 35 [Q2 set_COVID-19-ARDS cohorts _Neuroimaging_Brain Injury] (372)
37	34 or 36 (3537)
38	limit 37 to english language (3317)
39	38 not (exp Animals/ not (Human/ and exp Animals/)) (3278)
40	(mice or rat or rats or cat$1 or cattle$1 or dog$1 or goat$1 or horse$1 or rabbit$1 or sheep$1 or swine$1 or pig$1 or canine$1 or feline$1 or porcine$ or calf or (pediatr$ or paediatr$ or fetal or fetus or child$ or adolescent$ or infan$ or newborn$ or boy$1 or neonat$)).ti. (4361892)
41	39 not 40 (2825)
42	limit 41 to (adult <18 to 64 years> or aged <65+ years>) (1823)
43	limit 41 to (embryo <first trimester> or infant <to one year> or child <unspecified age>) (271)
44	41 not (43 not (42 and 43)) (2631)
45	exp case control study/ or (case$ and control$).tw,kw. or exp case study/ or (case$ and series).tw,kw. [EMBASE case series] (1287438)
46	case report/ or case report$.tw,kw. (2998972)
47	44 not (46 not (45 and 46)) (1185)
48	47 not case report.ti. [Removing case Reports and retaining Case Series] (1156)
49	limit 48 to embase (383)

Table A2. Comprehensive search strategy for Cochrane Central Register of Controlled Trials

Database	Cochrane Central Register of Controlled Trials
1	Respiratory Distress Syndrome/ (1524)
2	(respirator$ adj2 distress$ adj2 syndrom$).tw. (4239)
3	ARDS.tw. (2432)
4	((acute$ or adult$ or severe$) adj3 (respirator$ adj3 distress$)).tw. (2715)
5	(lung$ adj2 shock$).tw. (9)
6	(((post traumatic$ or posttraumatic$) adj3 (respirator$ or lung$)) and failure$).tw. (9)
7	((post traumatic$ or posttraumatic$) adj3 pulmonar$ adj3 insufficienc$).tw. (3)
8	exp Respiratory Insufficiency/ (3085)
9	((respirat$ adj3 (distress$ or failure$ or insufficien$ or paralysis$ or deficienc$ or disturbanc$ or depression)).tw. (13982)
10	(acute$ and ((respirat$ adj2 insufficienc$) or (respirat$ adj2 failure$))).tw. (2538)
11	Acute Lung Injury/ (577)
12	(acute$ and (lung$ adj2 injur$)).tw. (1376)
13	((lung$ or pulmonary$) adj3 (failure$ or insufficien$)).tw. (991)
14	or/1-13 (18021)
15	Critical Care/ or Critical Illness/ or (critical$ or intensive*).jn,jw. or critically$.tw. or (critical$ adj2 ill$).mp. (19278)
16	exp intensive care units/ or (ICU or ICUs or ((intensive care$ or intensive therapy$ or intensive treatment$ or high dependency$ or (coronary$ adj2 care$) or critical$ care) adj2 unit$) or MICU or CICU or CVICU or CCU$1 or SICU or POCCU$1 or HDU?ITU or ITU$1 or HDU$1).mp. or (critical$ and (intensive adj care)).mp. or (intensiv$ therap$ or intensiv$ treat$).tw. (35433)
17	exp Respiration, Artificial/ or exp Ventilators, Mechanical/ or (ventilat$ adj2 (artificial$ or mechanical$)).tw. or (respirat$ adj2 (artificial$ or assisted$ or mechanical$)).tw. or (respirat$ adj2 failure$).tw. (21088)
18	((ventilat$ adj2 (weaning or support$)) or ((positive adj3 pressure adj5 (ventilat$ or respir$)) or (PPV and (pressure or ventilat$)))).tw. or (ventilat$ adj3 patient$).ti. or (ventilat$ and patient$).ab. /freq=3 (13316)
19	or/15-18 (59572)

20	14 and 19 (9586)
21	exp diagnostic techniques, neurological/ (10421)
22	(neuronavigat$ or neuro-navigat$ or neuroimag$ or neuro-imag$ or (neurolog$ adj3 (evaluat$ or assess$ or examin$)) or neuroradiogr$ or neuro-radiogr$).tw. (6304)
23	(thickness$ adj3 (cortical$ or brain or cerebral$ or cortex$)).tw. (599)
24	Positron-Emission Tomography/ or "Fluorodeoxyglucose F 18"/ or (f-18$ or f18$ or fluorine-18$ or 18f$ or 18-f$ or fluorodeoxyglucose$ or FDG$).tw. (7447)
25	((PET$ or "P.E.T.") and (scan$ or imag$3 pr stag$ or F-18$ or f18$ or 18f$ or 18-f$ or fluorine-18$ or fluorodeoxyglucose$ or FDG$)).tw. (4582)
26	exp Magnetic Resonance Imaging/ (8991)
27	(magnetic resonance imag$ or imaging$ or mri$ or fMRI$ or (fluid?attenuat$ inversion$ recover$ or FLAIR)).tw. (59225)
28	exp Tomography, X-Ray Computed/ (5591)
29	((cat or ct$) adj2 (scan$ or x?ray or examination or imag$ or compute$ or diagnos$)).tw. (13395)
30	PET?CT.tw. (33)
31	or/21-30 (89327)
32	(cerebr$ or intra?cerebral$ or cortical$ or subcortical$ or sub-cortical$ or cortex or brain$ or neurolog$).mp. or exp Brain Diseases/ or (brain$ adj5 (disease$ or disorder$)).tw. (159256)
33	(hyperintens* or ((white$ or white?gr?y$) adj3 matter$) or lepto?mening$ or meningitis$ or meningo?encephalitis or demyelination or dysmyelination or myelitis or leukoencephalopath$ or encephal* or ADEM).tw. (9213)
34	or/32-33 (163095)
35	31 and 34 (33252)
36	20 and 35 (86)
37	(exp pneumonia/ or (pneumonia or covid* or coronavirus* or corona virus* or ncov* or 2019-ncov or sars*).mp.) and Wuhan.mp. (262)
38	(2019-ncov or ncov19 or ncov-19 or 2019-novel CoV or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or coronavirus-19 or covid19 or covid-19 or covid 2019 or ((novel or new or nouveau) adj2 (CoV on nCoV or covid or coronavirus* or corona virus or Pandemi*2)) or ((covid or covid19 or covid-19) and pandemic*2) or (coronavirus* and pneumonia)).mp. (13367)

39	or/37-38 (13372)
40	14 and 35 and 39 (7)
41	36 or 40 (86)
42	limit 41 to english language (86)
43	(mice or rat or rats or cat$1 or cattle$1 or dog$1 or goat$1 or horse$1 or rabbit$1 or sheep$1 or swine$1 or pig$1 or canine$1 or feline$1 or porcine$ or calf or (pediatr$ or paediatr$ or fetal or fetus or child$ or adolescent$ or infan$ or newborn$ or boy$1 or neonat$)).ti. (148703)
44	42 not 43 (66)

Appendix B: Cortical projection of brain injury frequency stratified by type of brain injury

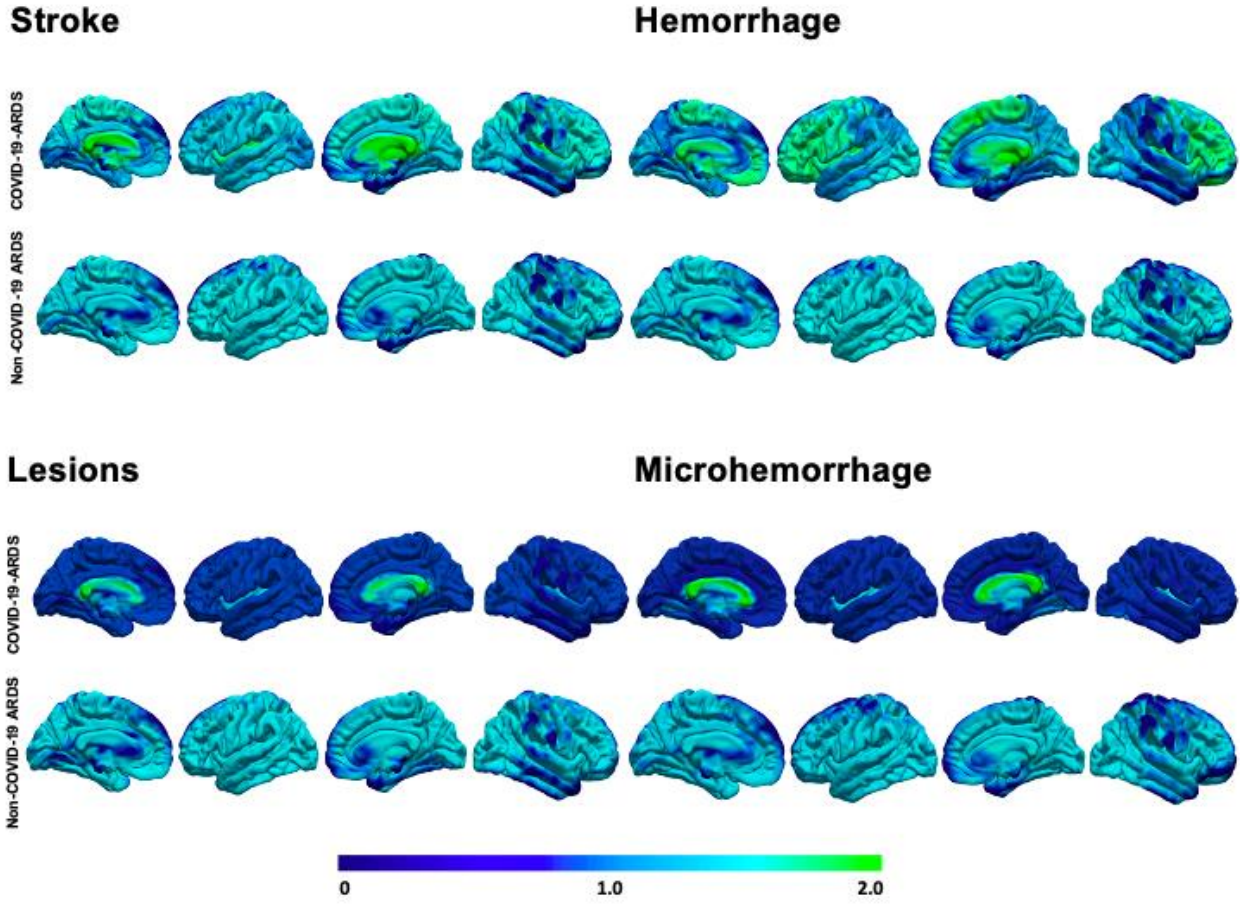


Figure A1. Brain injuries stratified by COVID-19 status and types of injuries

Appendix C: Additional meta-analyses of COVID-19 ARDS and non-COVID-19 ARDS neuroimaging findings

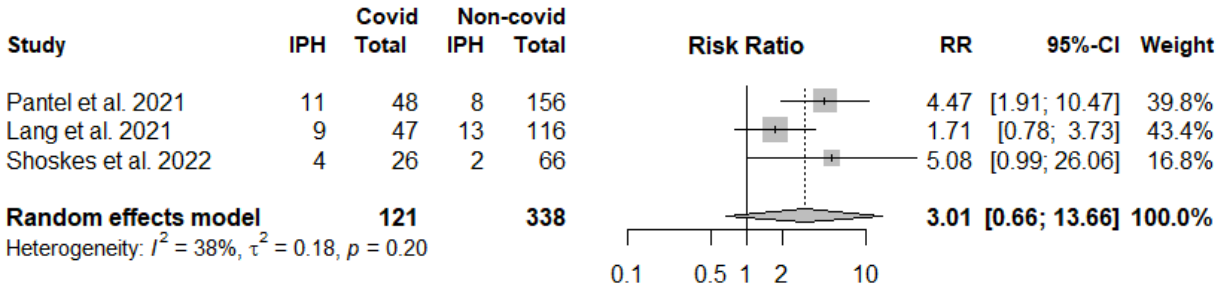


Figure A2. Risk for developing intraparenchymal hemorrhage (IPH) in COVID-19 ARDS versus non-COVID-19 ARDS

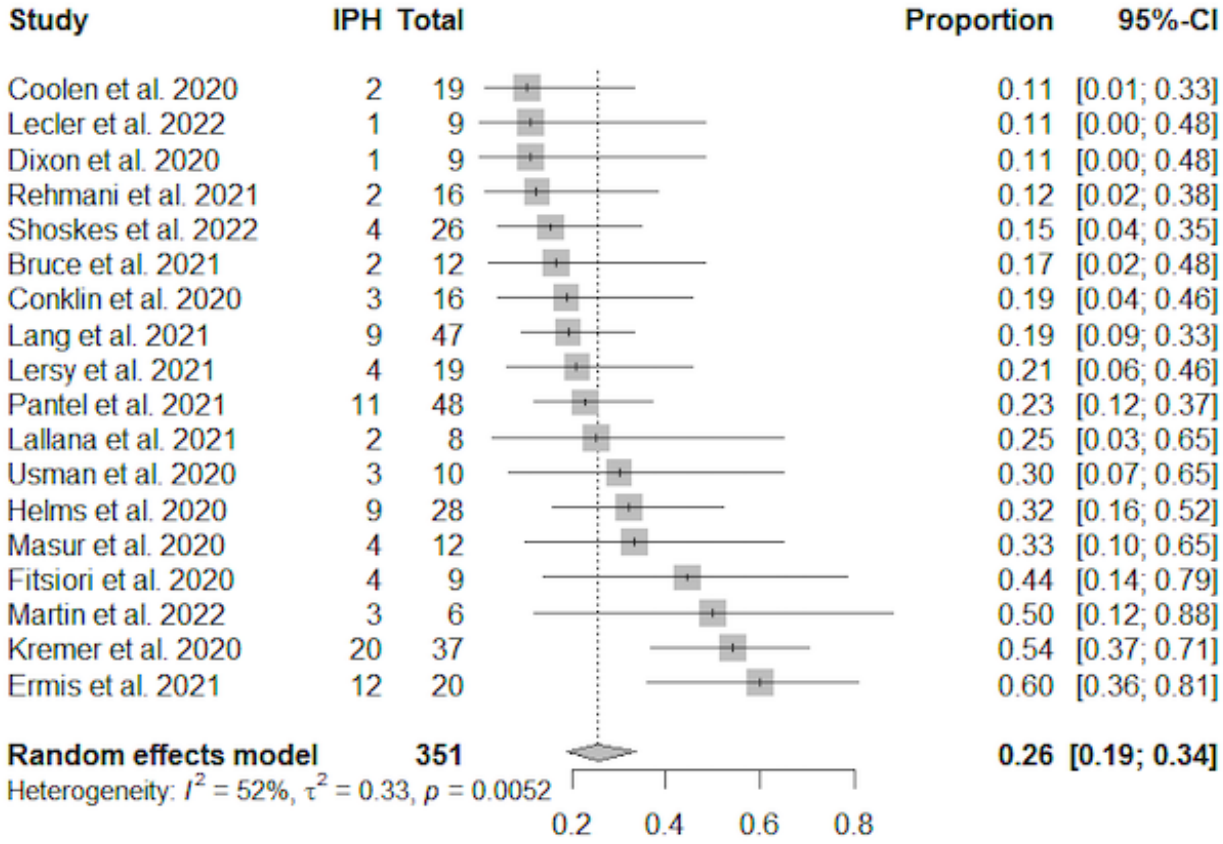


Figure A3. Meta-analysis of COVID-19 ARDS intraparenchymal hemorrhage (IPH) frequency, indicating pooled proportions

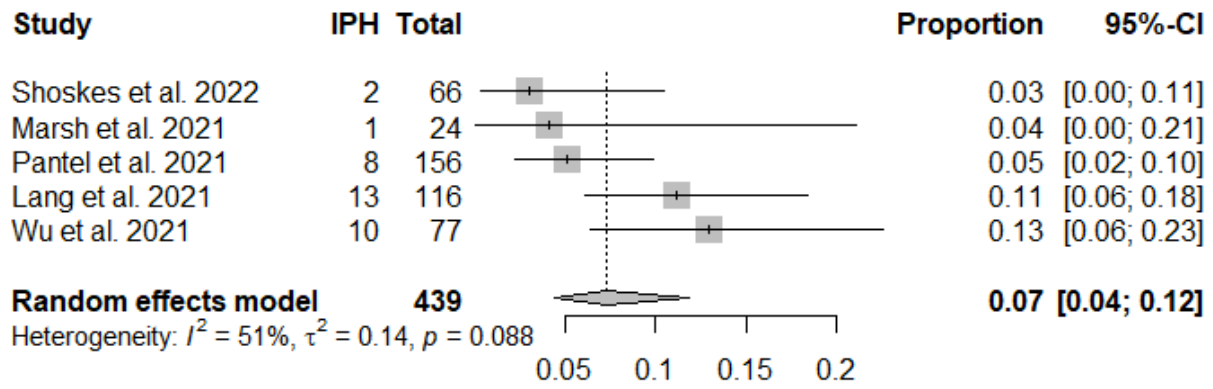


Figure A4. Meta-analysis of non-COVID-19 ARDS intraparenchymal hemorrhage (IPH) frequency, indicating pooled proportions

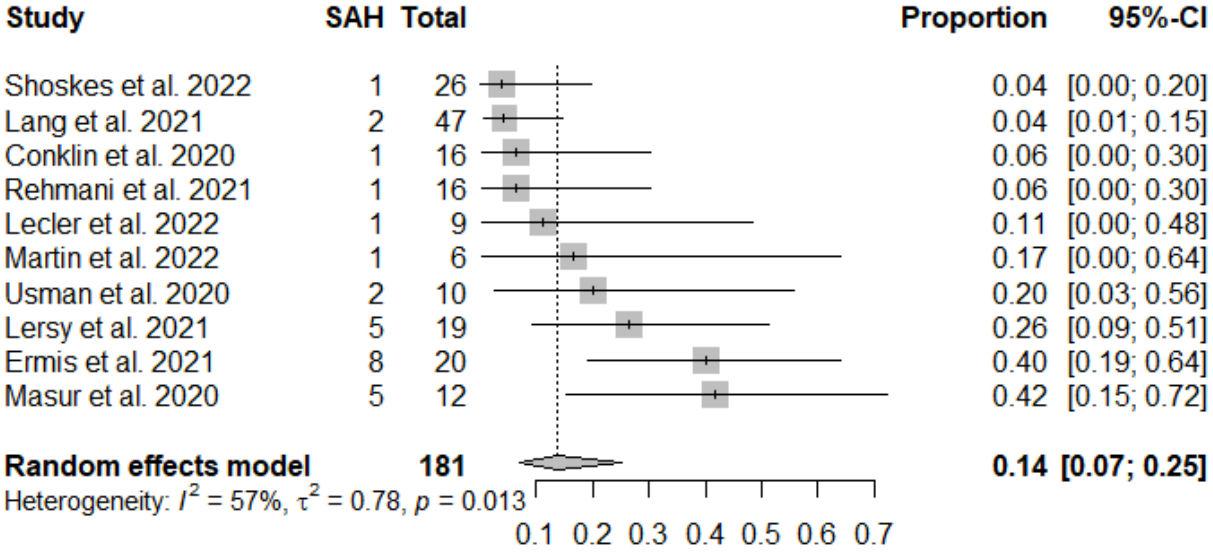


Figure A5. Meta-analysis of COVID-19 ARDS subarachnoid hemorrhage (SAH) frequency, indicating pooled proportions

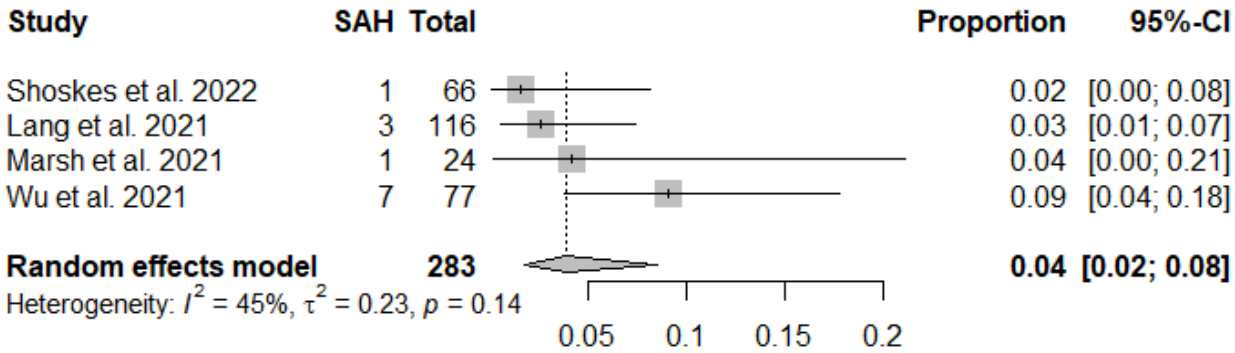


Figure A5. Meta-analysis of non-COVID-19 ARDS subarachnoid hemorrhage (SAH) frequency, indicating pooled proportions

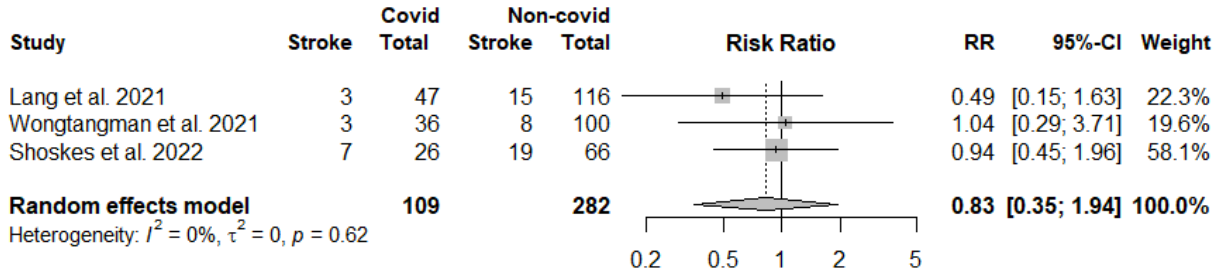


Figure A6. Risk for developing ischemic stroke in COVID-19 ARDS versus non-COVID-19 ARDS

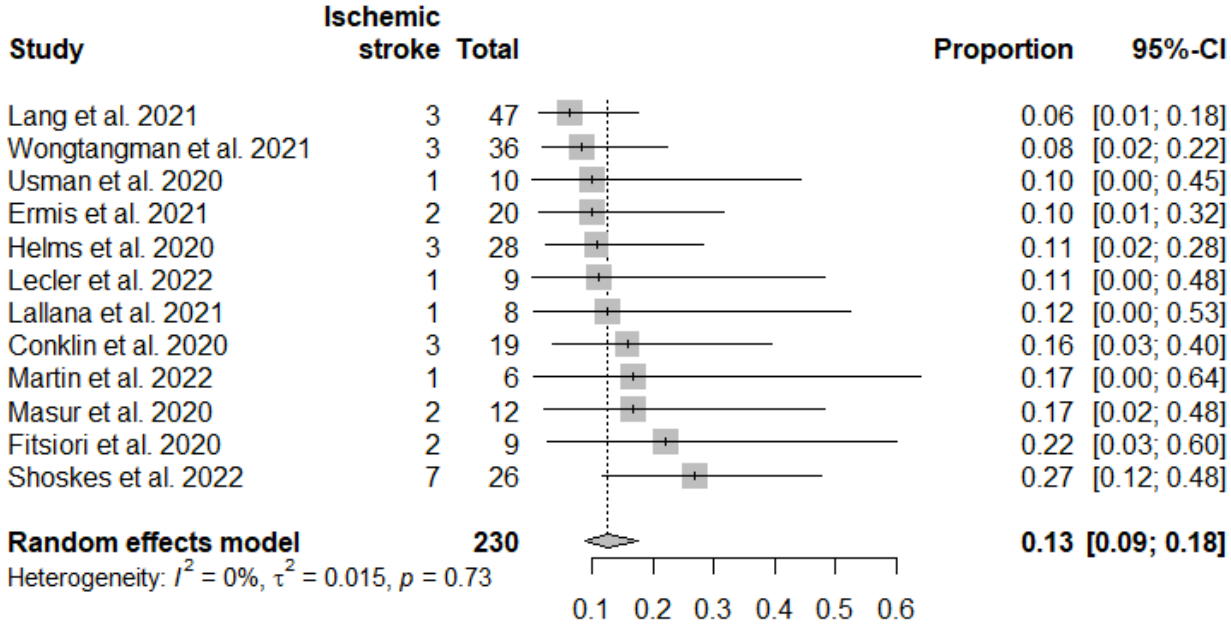


Figure A7. Meta-analysis of COVID-19 ARDS ischemic stroke frequency, indicating pooled proportions

Curriculum Vitae

Name: Rachel Wagner

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Publications:

Rachel Wagner, Michael T. Jurkiewicz, Jennifer Chen, Angela Jerath, Marat Slessarev, Udunna C Anazodo. Spectrum of Brain Injury in COVID-19 Acute Respiratory Distress Syndrome: A Systematic Review and Meta-Analysis. 2023, ISMRM, Toronto, Canada

Rachel Wagner, Michael T. Jurkiewicz, Jennifer Chen, Angela Jerath, Udunna C Anazodo, Marat Slessarev. Neurological Sequalae of COVID-19 Acute Respiratory Distress Syndrome. 2022, CCCF, Toronto, Canada

Rachel Wagner, Michael T. Jurkiewicz, Jennifer Chen, Angela Jerath, Marat Slessarev, Udunna C Anazodo. Brain Injury in COVID-19 Acute Respiratory Distress Syndrome: A Systematic Review of Neuroimaging Findings. 2022, London Imaging Discovery, London, Ontario, Canada