Neurocrit Care (2021) 35:518–527
https://doi.org/10.1007/s12028-021-01309-x

NEUROCRITICAL CARE SOCIETY

REVIEW ARTICLE

Pathophysiology of Brain Injury and Neurological Outcome in Acute Respiratory Distress Syndrome: A Scoping Review of Preclinical to Clinical Studies

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Abstract

Acute respiratory distress syndrome (ARDS) has been associated with secondary acute brain injury (ABI). However, there is sparse literature on the mechanism of lung-mediated brain injury and prevalence of ARDS-associated secondary ABI. We aimed to review and elucidate potential mechanisms of ARDS-mediated ABI from preclinical models and assess the prevalence of ABI and neurological outcome in ARDS with clinical studies. We conducted a systematic search of PubMed and five other databases reporting ABI and ARDS through July 6, 2020 and included studies with ABI and neurological outcome occurring after ARDS. We found 38 studies (10 preclinical studies with 143 animals; 28 clinical studies with 1175 patients) encompassing 9 animal studies ($n=143$), 1 in vitro study, 12 studies on neurocognitive outcomes ($n=797$), 2 clinical observational studies ($n=126$), 1 neuroimaging study ($n=15$), and 13 clinical case series/reports ($n=15$). Six ARDS animal studies demonstrated evidence of neuroinflammation and neuronal damage within the hippocampus. Five animal studies demonstrated altered cerebral blood flow and increased intracranial pressure with the use of lung-protective mechanical ventilation. High frequency of ARDS-associated secondary ABI or poor neurological outcome was observed ranging 82–86% in clinical observational studies. Of the clinically reported ABIs (median age 49 years, 46% men), the most common injury was hemorrhagic stroke (25%), followed by hypoxic ischemic brain injury (22%), diffuse cerebral edema (11%), and ischemic stroke (8%). Cognitive impairment in patients with ARDS ($n=797$) was observed in 87% (range 73–100%) at discharge, 36% (range 32–37%) at 6 months, and 30% (range 25–45%) at 1 year. Mechanisms of ARDS-associated secondary ABI include primary hypoxic ischemic injury from hypoxic respiratory failure, secondary injury, such as lung injury induced neuroinflammation, and increased intracranial pressure from ARDS lung-protective mechanical ventilation strategy. In summary, paucity of clinical data exists on the prevalence of ABI in patients with ARDS. Hemorrhagic stroke and hypoxic ischemic brain injury were commonly observed. Persistent cognitive impairment was highly prevalent in patients with ARDS.

Keywords: Acute respiratory distress syndrome, Acute brain injury, Neurological outcome, Lung-brain interaction

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This article is related to the Invited Commentary available at https://link.springer.com/article/10.1007/s12028-021-01310-4.

Introduction

Acute respiratory distress syndrome (ARDS) is characterized by diffuse inflammation and noncardiogenic pulmonary edema due to increased alveolar-capillary vascular permeability, which leads to severe hypoxemia and respiratory failure requiring mechanical

ventilatory support [1]. ARDS has a prevalence of 19 to 23% [2, 3] of all patients who are mechanically ventilated and carries a significant hospital mortality rate of 35 to 48% [2, 4, 5]. Survivors of ARDS have long-term morbidity, including ventilatory deficits, decreased physical function, and neuropsychiatric morbidities [1, 6–8].

Acute brain injury (ABI) can lead to development of ARDS. For instance, approximately one in four patients with isolated traumatic brain injury or spontaneous intracranial hemorrhage developed ARDS during hospitalization [9, 10]. On the other hand, ARDS can lead to ABI and thus impair neurological function. These observations suggest the existence of cross talk between the lung and the brain [11]. Currently, the mechanism of lung-mediated brain injury is not well understood. Given that lung injury may lead to profound hypoxia, such as in ARDS, it is plausible that highly metabolic organs, such as the brain, may be affected [12]. Further, lung injury leads to release of systemic inflammatory mediators that can cross the blood–brain barrier and cause cerebral dysfunction [13]. The use of mechanical ventilation in lung injury may also alter serum carbon dioxide concentrations, which, in turn, can affect cerebral hemodynamics [14].

To date, there has not been a comprehensive effort to review ABI and neurological outcome in patients with ARDS. Furthermore, sparse evidence exists on the mechanisms of ARDS-associated secondary ABI. Herein, we aimed to (1) review preclinical studies of ARDS-associated secondary ABI to understand the pathophysiology of ARDS-mediated brain injury and (2) review clinical studies of ARDS-associated secondary ABIs and neurological outcome to understand the prevalence of ABI in patients with ARDS.

Methods

Search Strategy

This scoping review was reported following the framework described in Arksey and O'Malley [15] and according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [16]. We searched PubMed, both legacy and new, via NCBI, Embase via Elsevier, the Cochrane Library via Wiley, Web of Science Core Collection via Clarivate, and Scopus via Elsevier. The search included controlled vocabulary subject headings and keywords related to ARDS and ABI from inception to July 6, 2020. An effort was made to account for plurals, acronyms, and synonyms. The detailed search strategy is available in Appendix 1. The results were deduplicated and uploaded to Covidence.

Inclusion Criteria

Inclusion criteria were applied following the population, intervention, comparator, outcome, and study design approach [16]. We included (1) randomized controlled trials (RCTs), observational studies, case series/reports, and animal and in vitro studies; (2) adult patients (>18 years); (3) ARDS defined by the Berlin Criteria or American-European Consensus Conference Criteria [17, 18]; and (4) studies with ABI occurring after ARDS. The search was not limited to English language, and non-English articles were translated and reviewed for inclusion eligibility.

Exclusion Criteria

We excluded (1) editorials, commentaries, and reviews; (2) studies with ABI occurring after implementation of ECMO for ARDS because of an increased risk of ABI in this patient cohort [19]; (3) studies with acute lung injury that did not meet ARDS criteria; and (4) studies with ABI occurring prior to ARDS.

Study Selection and Data Extraction

Two reviewers (MH, AG) independently assessed the literature results for eligibility. A third reviewer (CH or SM-C) resolved any disagreements on inclusion/exclusion of the literature. Covidence, Cochrane's online systematic review platform, was used to streamline the review process. Articles meeting inclusion criteria were retrieved and the full text was reviewed. References of included studies were screened and included based on inclusion and exclusion criteria. Data from eligible articles were extracted and recorded in an excel spreadsheet (Microsoft, Redmond, WA). Extracted data included authors, title of article, date of publication, name of journal, type of article, objectives, methods, key findings, brain injury, neurological outcome, sample size, demographics, hospital length of stay, ARDS severity, PaO_2 to FiO_2 ratio, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, and other quantitative results, if applicable.

Primary Outcomes

Primary outcomes were mechanisms of ARDS-mediated secondary ABI. Clinical outcomes were ABI and neuroimaging abnormalities reported during index hospitalization and neurological outcome at discharge and follow-up. ABI included hypoxic ischemic brain injury (HIBI), ischemic stroke, and hemorrhagic stroke. Neuroimaging abnormalities included brain atrophy and cerebral microbleed (CMB). Neurological outcomes included cognitive function and Cerebral

Performance Category score (defined as favorable neurological outcome if <3).

Quality Assessment and Risk of Bias

The Cochrane Risk of Bias assessment tool was used to assess risk of bias in RCT in eight domains [20]. The trial was considered high risk if at least one domain was rated as a high risk and low risk if all domains were judged as low. The Newcastle–Ottawa Scale (NOS) was used to evaluate the risk of bias of cohort studies. The NOS scores assigned points to three domains: patient selection, comparability, and assessment of outcome or exposure [21]. Studies scoring 6 or more points were considered to have a low risk for bias. The Murad tool was used to assess the quality of case reports/series [22]. The study was considered to be high quality if it had adequate data in selection, ascertainment, causality, and reporting. Publication quality was assessed independently by two investigators (MH, AG). Any discrepancies were resolved in consensus with a third investigator (CH).

Statistical Analysis

Data on age from all studies were collected and reported as an overall median. The portion of cognitive impairment was collected across all cognitive studies and reported as a median and range. The prevalence of ABI was calculated based on the number of patients with ABI divided by the total number of patients with ARDS. Meta-analysis of these studies was not performed because of limited number of studies and high heterogeneity of the included studies.

Results

The search yielded 31,327 citations. After 17,414 duplicates were removed, 13,913 citations remained. Following abstract screening, 382 articles were eligible for full text review. Of these studies, 344 were excluded based on exclusion criteria, including 3 studies with overlapping patient data, leaving the final 38 studies (10 preclinical studies with 143 animals; 28 clinical studies with 1032 patients) for the systematic review (Fig. 1), including 9 animal studies ($n=143$), 1 in vitro study, 12 studies on neurological cognitive outcomes ($n=797$), 2 clinical observational studies ($n=126$), 1 neuroimaging study ($n=15$), and 13 clinical case series/reports ($n=15$). A summary of the included studies is described in Supplemental Table 1.

Preclinical Animal and In Vitro Studies

Of the ten preclinical studies, nine studies ($n=143$) involved porcine with ARDS and one study was in vitro. ARDS was induced by one of three methods: (1) injection of oleic acid directly causing lung injury, (2) repeated pulmonary lavage causing surfactant depletion and poor gas exchange, or (3) hydrochloric acid aspiration directly causing lung injury.

Six animal studies ($n=100$) demonstrated neuroinflammation after ARDS with increased serum inflammatory markers, including interleukin-6 and tumor necrosis factor α, which correlated with elevated markers of neuronal damage, including neuron-specific enolase and S100 calcium-binding protein B [23–28]. Two studies ($n=12$) directly showed neuronal damage and perivascular inflammation in the pyramidal layer of the hippocampal region on both light microscopy and histopathological analysis in ARDS animals [24, 29].

Five studies ($n=59$) described adverse effects of mechanical ventilation in ARDS, including increased intracranial pressure (ICP), neuroinflammation, and disruption of cerebral oxygen metabolism [23, 26, 30, 31]. In one study, elevated plateau pressure was most strongly correlated with increased ICP when monitored with intraparenchymal Camino ICP monitoring device, followed by increased $PaCO_2$ and increased central venous pressure (CVP) [32]. Concomitant intraabdominal pressure through induction of pneumoperitoneum in lung injury was associated with further increases in ICP secondary to increased plateau pressure and CVP [32]. One in vitro study demonstrated neuronal secretion of inflammatory markers and apoptosis, in which these cells were mixed with the medium from lipopolysaccharide-induced injured airway epithelial cells [27]. Potential mechanisms of brain injury in ARDS in preclinical models are summarized in Table 1 and graphically represented in Fig. 2.

Clinical Studies on Brain Injury After ARDS

Observational Studies

There was a paucity of literature on ARDS-associated secondary brain injury, with only two observational studies ($n=126$). Among these studies, the median age was 61 year (63% men) and 53% of the patients had sepsis or pneumonia. Severe ARDS was most common (43%), followed by moderate (40%) and mild ARDS (17%). High frequency of ABI or poor neurological outcome after ARDS was observed ranging 82–86%. Because of the heterogeneity and scarcity of reported outcomes, a cumulative statistical analysis on neurological outcome involving these two clinical studies was not preformed. One autopsy study ($n=7$) found HIBI to be the most common ABI (86%) after ARDS [33]. Another study found poor neurological outcome at 28 days was more frequently seen in patients with cardiac arrest with ARDS (82%), compared with those without ARDS (61%) [34].

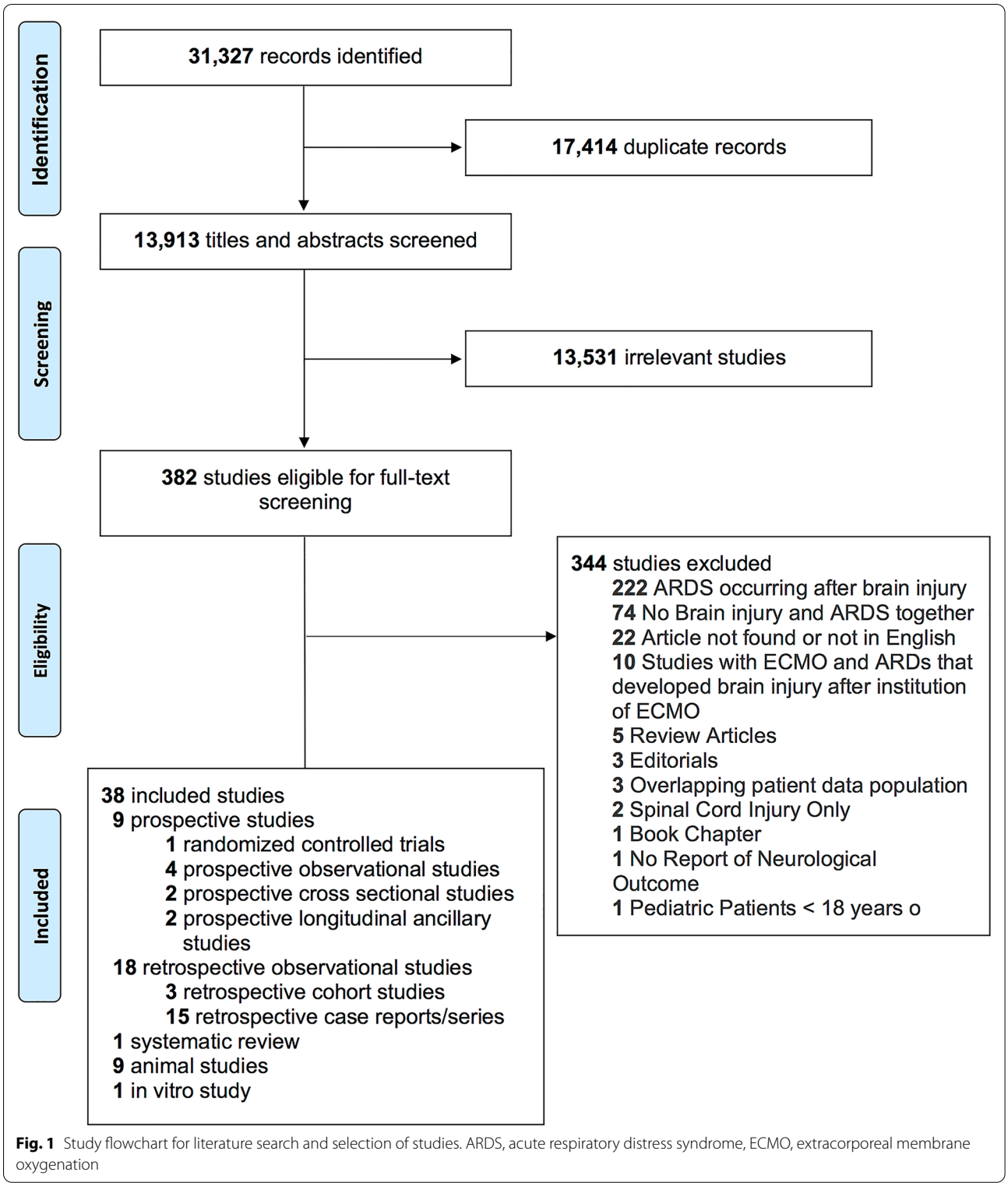

Fig. 1 Study flowchart for literature search and selection of studies. ARDS, acute respiratory distress syndrome, ECMO, extracorporeal membrane oxygenation

Table 1 Potential mechanisms of brain injury in acute respiratory distress syndrome in preclinical models

Neuroinflammation Study	Animal	*n*	Age, sex, weight	Lung injury method	Result
Bickenbach et al. 2011 [24]	Porcine	10	Female sex, 31.8 ± 1.2 kg	RBL	Increased serum IL-6 Inflammation on brain pathology
Fries et al. 2005 [29]	Porcine	14	Female sex, 29 ± 2 kg	RBL	Increased serum S100B Shrunken neurons of the pyramidal cell layer in the hippocampal CA1 on pathology
Heuer et al. 2011 [25]	Porcine	28	Female sex, 52–65 kg	OAI	Increased serum NSE Damage to the hippocampus and cerebral edema on pathology
Kamuf et al. 2017 [28]	Porcine	32	NA	OAI	Decreased in IL-6 expression in the brain with treatment of antiinflammatory agent
Rodriguez-Gonzalez et al. 2015 [27]	In vitro	NA	LPS induced alveolar cell injury	NA	Increased cellular secretion of S100B, NSE, IL-6 Neuronal necrosis and apoptosis
Adverse effects of lung-protective mechanical ventilatory strategy					
Bickenbach et al. 2009 [23]	Porcine	10	Female sex, 30.2 ± 2.0 kg	RBL	HT ventilation leads to increased serum S100B, IL-6, venous O2 concentration, and cerebral lactate levels
Kamuf et al. 2018 [26]	Porcine	20	Male sex, 24–31 kg	OAI/RBL	MV results in increased IL-6 and TNFα expression in hippocampus
Klein et al. 2013 [30]	Porcine	12	Juvenile, 25–27 kg	RBL	MV induced cyclic oscillations in peripheral PaO2 are transmitted to cerebral PaO2
Kreyer et al. 2013 [31]	Porcine	9	38.2 ± 5.3 kg	HA	LT ventilation results in hypercapnia and increased regional CBF
Zampieri et al. 2011 [32]	Porcine	8	Female sex, 35–42 kg	RBL	Plateau airway pressure, CO2 arterial pressure, and CVP are associated with increased ICP

CA1, cornu ammonis, CBF, cerebral blood flow, CVP, central venous pressure, HA, hydrochloric acid aspiration, HT, high tidal, ICP, intracranial pressure, IL-6, interleukin-6, LT, low tidal, LPS, lipopolysaccharide, MV, mechanical ventilation, NA, not available, NSE, neuron specific enolase, OAI, oleic acid injection, PaO2, partial pressure of oxygen, pECLA, percutaneous extracorporeal lung assist, RBL, repetitive bronchoalveolar lavage, R/D, recruitment/derecruitment, S100B, calcium-binding protein B, S100 calcium binding protein, TNF, tumor necrosis factor

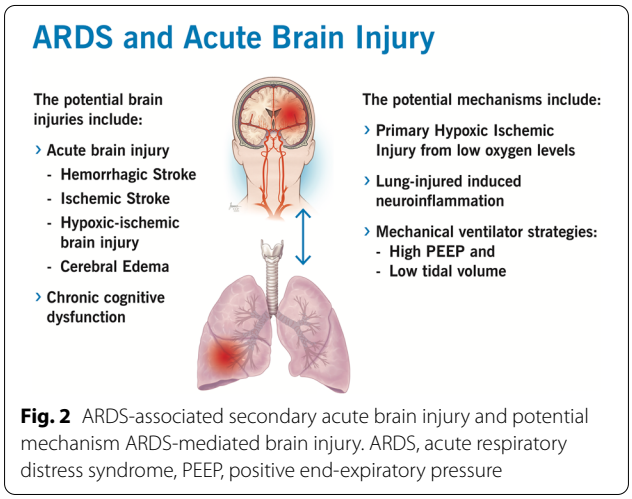

Fig. 2 ARDS-associated secondary acute brain injury and potential mechanism ARDS-mediated brain injury. ARDS, acute respiratory distress syndrome, PEEP, positive end-expiratory pressure

Case Reports/Case Series

Among case reports/series (13 studies, $n=15$), the median age was 49 years (33% men) and 87% ($n=13$) suffered from sepsis. Of these patients who were septic, 77% ($n=10$) had ARDS secondary to respiratory viral illness, including seven H1N1, two SARS-CoV-2, and one MERS-CoV. Among the studies that reported ARDS severity ($n=4$), severe ARDS was the most common (75%), and 57% died from ARDS and its complications. The most common reported ABI was hemorrhagic stroke (40%), followed by diffuse cerebral edema (20%), HIBI (13%), and ischemic stroke (13%). Of the patients with hemorrhagic stroke, 33% had CMBs. Other ABIs included posterior reversible encephalopathy syndrome and delayed posthypoxic leukoencephalopathy. A summary of reported clinical brain injuries in all case reports and clinical studies of ARDS is described in Table 2 and graphically represented in Fig. 2.

Neuroimaging Studies

There was only one neuroimaging study ($n=15$) involving head computed tomography of patients with ARDS, with a median age of 39.2 years (60% men). Severity and etiology of ARDS were not reported. Brain atrophy was

Table 2 Types of reported acute brain injuries in ARDS

Characteristics	Patients with ARDS and ABI (*n* = 30)
Demographics	
Age, median (IQR)	50 (44–54)
Male sex	8 (30%)
Past medical history	
Lung disease	8 (33.3%)
Malignancy	3 (12.5%)
Obesity	3 (12.5%)
Smoking	2 (8.3%)
Hypertension	1 (4.2%)
Atrial fibrillation	1 (4.2%)
Hypothyroidism	1 (4.2%)
Alcohol use	1 (4.2%)
Cardiac disease	1 (4.2%)
Diabetes	1 (4.2%)
Other	2 (8.3%)
Etiology of ARDS	
Sepsis or pneumonia	19 (95%)
Drug reaction	1 (5%)
ARDS variables	
Mild ARDS	1 (8.3%)
Moderate ARDS	0 (0%)
Severe ARDS	11 (91.7%)
Types of ABI	
Brain atrophy	9 (25%)
Hypoxic ischemic brain injury	8 (22.2%)
Subarachnoid hemorrhage	5 (13.9%)
Cerebral edema	4 (11.1%)
Ischemic stroke	3 (8.3%)
Intracranial hemorrhage	2 (5.6%)
Critical-illness associated microbleeds	2 (5.6%)
Delayed posthypoxic leukoencephalopathy	2 (5.6%)
Posterior reversible leukoencephalopathy	1 (2.8%)
Survival	14/30 (47%)

Male gender, past medical history, etiology of ARDS, and ARDS variables were not reported in all studies; percentages are of all patients in all studies which reported these variables

ABI, acute brain injury, ARDS, acute respiratory distress syndrome, IQR, interquartile range

the most common finding on head computed tomography (53%) with prominent involvement of the hippocampus (71%) [35].

Clinical Studies on Neurological and Cognitive Outcomes

The observational studies on cognitive outcome in ARDS included 797 patients (median age: 46 years, 45% men). The most common cognitive assessments used were Wechsler Adult Intelligence Scale-Third Edition and Weschler Memory Scale-Third Edition. A full list of cognitive assessment tools used in these studies is listed in Supplemental Table 2. The median hospital stay in all patients was 38.9 days, median intensive care unit (ICU) stay was 14.6 days, and median duration of intubation was 19.7 days. Median PaO_2 to FiO_2 ratio at admission was 154.7 and median APACHE II score at admission was 21 (Supplemental Table 3). The median proportion of cognitive impairment across all studies was 87% (range 73–100%) at discharge, 36% (range 32–37%) at 6 months, and 30% (range 25–45%) at 1 year (Table 3). Among the studies, cognitive impairment was not found to be associated with age, sex, APACHE II, hospital or ICU duration, mechanical ventilation duration, or use of sedatives, narcotics, and paralytics. Two studies found cognitive impairment was associated with hypotension (mean arterial pressure <50 mm Hg) during ICU stay and low PaO_2 on admission (71 mm Hg) [36, 37]. One study found low CVP and conservative fluid management in ARDS were associated with cognitive dysfunction, possibly due to decreased cerebral perfusion [37]. Another study found hyperglycemia (highest glucose levels >153.5 mg/dL) during ICU stay was associated with cognitive impairment [38]. A summary of associated factors in the development of cognitive impairment following ARDS is described in Supplemental Table 4.

Risk of Bias Assessment

The Cochrane tool showed high risk of bias for three animal RCTs because of inadequate information regarding randomization. The remainder of RCTs were low risk (Supplemental Table 5). The NOS was conducted on two cohort studies and did not indicate high risk of bias for any study with median NOS score of 6.5 (Supplemental Table 6). All included case series had adequate data on case selection, exposure and outcome ascertainment, and causality, with a median score of 6.

Discussion

We performed a scoping review on both preclinical and clinical studies reporting ABI and neurological outcome in ARDS to better understand the pathophysiology behind ARDS-mediated secondary brain injury and to assess the prevalence of clinical ARDS-associated secondary. Our review found evidence of neuroinflammation and altered cerebral hemodynamics with use of mechanical ventilation in preclinical animal studies with ARDS. There was an overall paucity of clinical reports on ARDS-associated secondary ABIs. However, we found a high frequency of ABI based on few observational studies. Types of reported ABI in patients with ARDS were hemorrhagic stroke including intracerebral hemorrhage, subarachnoid hemorrhage, and CMB, ischemic injury

Table 3 Studies on cognitive impairment in acute respiratory distress syndrome

Study	Type of study	*n*	Age	Male sex	Cognitive impairment
Cognitive impairment at discharge					
Hopkins et al. 1999 [36]	Prospective observational study	55	46	25	100%
Hopkins et al. 2004 [64]	Prospective observational study	74	46	33	73%
Cognitive impairment at 6 months			Median (IQR):	87% (73–100%)	
Jackson et al. 2003 [67]	Prospective observational study	34	53	18	32%[a]
Needham et al. 2013	Prospective observational study	174	47	87	36%
Needham et al. 2016	Randomized controlled trial	189	50	89	37%
Cognitive impairment at 1 year			Median (IQR):	36% (32–37%)	
Hopkins et al. 1999 [36]	Prospective observational study	55	46	25	30%
Hopkins et al. 2004 [64]	Prospective observational study	74	46	33	46%
Mikkelsen et al. 2012 [37]	Prospective observational study	75	50	32	55%
Needham et al. 2013	Prospective observational study	174	47	87	25%
Needham et al. 2016	Randomized controlled trial	189	50	89	29%
Cognitive impairment at 2 years			Median (IQR):	30% (25–45%)	
Adhikari et al. 2009	Prospective observational study	71	42	38	8–20%[b]
Mikkelsen et al. 2009	Prospective cross-sectional study	79	43	12	56%
Cognitive impairment at 6 years					
Rothenhäusler et al. 2001	Retrospective study	46	NA[c]	24	24%

IQR, interquartile range, WAIS-III

[a] Percent decline from premorbid subindices of WAIS-III

[b] Range reported based on varying definition of memory loss used

[c] Age was reported in ranges and not as overall composite

including ischemic stroke and HIBI, diffuse and focal hippocampal brain atrophy, and diffuse cerebral edema. Less commonly reported ABIs were posterior reversible encephalopathy syndrome and delayed posthypoxic leukoencephalopathy.

Our study suggests, based on preclinical studies, that ARDS induced ABI is mediated through two major mechanisms: (1) neuroinflammation and (2) neurological adverse effects of lung-protective mechanical ventilation strategy. First, direct alveolar stretching and lung injury have been shown to promote release of proinflammatory cytokines, including TNF-alpha, IL-1beta, and IL-6 [11, 24–26, 39, 40]. Such inflammation can directly cause neuronal apoptosis [41]. Interestingly, the hippocampal region has a high density of IL-1 receptors, which may explain the common occurrence of hippocampal injury seen in patients with ARDS given its vulnerability to inflammation as well as hypoxic insult [42]. Second, although ARDS mechanical ventilatory strategies have demonstrated to improve survival, they may contribute or worsen brain injury in some patients [14, 43, 44]. Lung-protective strategy with low tidal ventilation to reduce lung strain is associated with hypercapnia and subsequent cerebral vasodilation, increased cerebral blood flow, and increased ICP, which may further worsen ABI and increase risk for cerebral ischemia [14]. High positive end-expiratory pressure (PEEP) is another ventilation strategy used in ARDS to improve oxygenation, prevent alveolar collapse, and reduce atelectrauma [45]. Theoretically, high PEEP may cause increased ICP through multiple mechanisms, including (1) increased cerebral vasodilation from elevated intrathoracic pressure and subsequent decrease in mean arterial pressure (2) decreased cerebral venous outflow from increased CVP, and (3) reduced cerebrospinal fluid outflow from increased spinal pressure [46]. However, previous animal and human studies did not reveal that PEEP had such effect an on ICP although these studies did not involve subjects with ARDS who may have decreased lung compliance and therefore be more sensitive to intrathoracic transmission of PEEP [46, 47]. One ARDS animal study found plateau pressure, CVP, and $PaCO_2$ were associated with increased ICP [32]. Further, ARDS animals with concomitant increased intraabdominal pressure

had greater increases in ICP compared with lung injured animals alone, likely due to greater elevation in plateau pressure. A recent clinical study also found that high lung compliance is associated with favorable neurological outcome in patients with ARDS [48]. It is therefore plausible that select patients with decreased lung compliance such as in ARDS may be more sensitive to effects of PEEP on ICP, particularly when combined with low tidal ventilation leading to permissive hypercapnia and subsequent cerebral vasodilation. However, further clinical research on the effects of PEEP on ICP in patients with elevated plateau pressure is needed.

Our study demonstrated that the most common clinical ABI after ARDS was hemorrhagic stroke (25%). The mechanism of hemorrhagic stroke in patients with ARDS is not entirely clear given limited reporting. One potential mechanism can be elucidated from occurrence of CMBs in patients with ARDS. Two ARDS case reports showed diffuse CMBs predominantly involving the cerebellum, brainstem, and juxtacortical white matter with sparing of the cortex, which may be consistent with Critical Illness Associated Microbleeds [49, 50]. These CMBs are thought to be due to hypoxemia and inflammation causing endothelial dysfunction, breakdown of blood–brain barrier, and subsequent extravasation of erythrocytes [51]. ARDS is characterized by hypoxemia and an increased systemic inflammatory state, which can result in endothelial dysfunction and therefore contribute to CMBs, a phenotype of cerebral small vessel disease [51–53], which may further evolve to hemorrhagic stroke during acute illness.

Ischemic brain injury was also commonly observed in ARDS. The mechanisms of ischemic stroke included watershed infarcts in the setting of septic shock and gas emboli secondary to barotrauma from mechanical ventilation [33, 54]. An autopsy study on patients with ARDS showed that HIBI was most commonly observed in hippocampus, specifically the pyramidal neurons in the CA1 region [33]. The hippocampus is known to be selectively vulnerable to ischemic injury due to high metabolic demand [55, 56]. Possible mechanisms of HIBI include prolonged hypoxemia from impaired exchange, particularly those with severe-refractory ARDS, and hypotension secondary to concomitant sepsis and shock physiology in ARDS. These factors disrupt oxygen and glucose delivery to brain tissue, leading to mitochondrial dysfunction and failure of energy-dependent ion chains subsequently causing neuronal apoptosis, necrosis, and cytotoxic edema [57]. Several cases of cerebral edema were reported in patients with ARDS, likely resulting from consequences of HIBI [58–60]. Diffuse cerebral atrophy was also commonly reported in patients with ARDS [35] although it is uncertain if this was caused by acute inflammation or hypoxemia from ARDS due to the absence of pre-ARDS imaging studies as a control. However, previous studies have described cerebral atrophy in patients with chronic hypoxemia, such as in obstructive sleep apnea and chronic obstructive pulmonary disease [61, 62]. Additionally, brain atrophy has been observed in patients following cardiac arrest [63]. Further research is needed to assess the severity of ARDS and its impact on ischemic ABI.

It is important to highlight that survivors of ARDS commonly suffer from short-term and long-term cognitive impairment including memory, attention, and concentration domains [36]. Hypotension and hypoxemia were important risk factors associated with cognitive impairment [37, 64]. Decreased perfusion and refractory hypoxia may injure areas vulnerable to ischemic insult including hypothalamus, thalamus, and areas of the cortex, all of which are closely involved in neurocognitive function [63]. We found that cognitive function in ARDS survivors did not improve at 1–2 years after ARDS [65] and patients who did not recall their ICU stay or had fewer years of education (14.1 vs. 11.3 years) had greater degree of cognitive dysfunction [64, 66, 67]. Despite the common occurrence of long-term cognitive impairment in ARDS survivors, sparse data exist on preventative and therapeutic interventions to mitigate poor cognitive outcome in ARDS.

Our study has several limitations. First, the paucity of available studies and high degree of heterogeneity across both clinical and preclinical studies limit our ability to adequately assess the prevalence of ARDS-associated ABI. Further, it is possible that the prevalence of ABI may have been overestimated given that the included studies assessed more patients who were critically ill. Conversely, ABI may be underestimated given that it can be underrecognized by clinicians [2, 68]. As the severity of ARDS was not consistently reported, the impact of ARDS severity on ABI and neurological outcome could not be accurately assessed. Also, included studies did not report some important factors such as stroke risk factors that may have confounded the reported ABIs. A recent systematic review demonstrated that delirium and cognitive impairment were associated with mechanical ventilation, and therefore, it is possible that poor neurological outcome may be attributed to mechanical ventilation alone [69]. However, that study was not focused on subjects with ARDS and our study only included animals and patients with ARDS and provides a comprehensive review of ABI after ARDS. Second, cognitive assessment tools varied among different studies with significant heterogeneity and the interpretation of the data should be done with caution. These ARDS cognitive studies also lacked control group without baseline assessment prior

to critical illness. Additionally, no studies accounted for ABIs in the development of cognitive impairment. Third, many case reports/series of ARDS included upper respiratory viral infection and sepsis leading to additional medical problems, which may have also contributed to ABIs. However, the animal studies without sepsis have robustly demonstrated the evidence for neuroinflammation in ARDS. Lastly, there were three animal RCTs that were determined to have high risk bias due to unclear randomization process. We included these studies in our review given that randomization was used to determine type of lung injury method to generate ARDS animal model, which did not have any effect on our outcome in reviewing the pathophysiology of ARDS-mediated brain injury.

Conclusions

Preclinical studies suggest that mechanisms of ARDS-associated ABI include primary hypoxic ischemic injury from hypoxic respiratory failure and secondary injury from lung injury induced neuroinflammation and increased ICP from lung-protective mechanical ventilatory strategies.

Paucity of clinical data exists on prevalence of ABI in patients with ARDS. Hemorrhagic stroke, HIBI, and brain atrophy were most observed ABIs. ARDS survivors have a high prevalence of cognitive impairment that may persist at 2 years.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1007/s12028-021-01309-x.

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Author contributions

Study concept and design: MH, SMC. Acquisition, analysis, or interpretation of data: MH, AG, CEH, THF. Statistical analysis: MH. Tables and figures: MH. First drafting of the article: MH, SMC. Critical revision for important intellectual content and final approval of the article: CMC, KU, RSS, PN. All authors approve of the final manuscript.

Conflict of interest

The authors declare that they have no conflicts of interest.

Ethical approval

All ethical guidelines and use of informed consent where applicable were followed.

Publisher's Note

Received: 21 April 2021 Accepted: 21 June 2021
Published online: 23 July 2021

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