

# Pathophysiology of Cerebral Microbleeds in Patients with Severe Respiratory Failure and Acute Respiratory Distress Syndrome: A Scoping Review

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**Abstract:** Cerebral microbleeds (CMBs) are increasingly identified in critically ill patients with severe respiratory failure and acute respiratory distress syndrome (ARDS). This scoping review aims to systematically examine the existing literature to explore the mechanisms contributing to the development of CMBs in ARDS and to summarize current evidence on CMBs associated with severe respiratory failure. We conducted a comprehensive search across two databases, PubMed and CENTRAL, and relevant study registries (PROSPERO and Clinicaltrials.gov), between February 1 and March 3, 2025. Eligible studies included those reporting on the presence of CMBs in adult patients with severe respiratory failure or ARDS, regardless of whether mechanical ventilation (MV) was used. Eighteen observational studies involving critically ill patients with respiratory failure or ARDS were included, with sample sizes ranging from 9 to 214 patients. The proposed pathophysiological mechanisms for the development of CMBs include hypoxaemia and inflammation leading to endothelial injury and blood–brain barrier (BBB) dysfunction, cerebral hypoperfusion facilitating interaction between coronavirus disease 2019 (COVID-19) and angiotensin-converting enzyme 2 (ACE2) receptors, microangiopathy with the formation of diffuse microthrombi, and renal failure contributing to uraemia-associated BBB disruption. CMBs were predominantly localized in the corpus callosum and juxtacortical white matter. The majority of patients with CMBs were mechanically ventilated and experienced a prolonged duration of ventilation. Identified risk factors for CMBs development included greater disease severity, coagulation abnormalities, and renal dysfunction. In conclusion, CMBs are increasingly recognized in critically ill patients with ARDS, particularly in the corpus callosum and juxtacortical white matter, but current evidence is associative rather than causal. Their pathophysiology likely involves compromised small vessel integrity due to hypoxia-induced endothelial injury, inflammation, and possible direct viral effects on cerebral microvasculature. These mechanisms are further exacerbated by coagulation abnormalities and disruption of the BBB.

**Keywords:** acute respiratory distress syndrome, cerebral microbleeds, coagulation abnormalities, hypoxaemia, inflammation, lung injury, mechanical ventilation

## Introduction

Acute respiratory distress syndrome (ARDS) is a significant contributor to morbidity and mortality among Intensive Care Unit (ICU) patients.<sup>1</sup> Defined by bilateral pulmonary infiltrates and refractory hypoxaemia,<sup>2</sup> ARDS not only inflicts severe pulmonary symptoms but also exerts extra-pulmonary consequences, such as hepatocellular dysfunction, acute coronary syndromes, acute kidney injury, and cognitive dysfunction.<sup>3–6</sup> Indeed, hypoxaemia has been implicated in inducing tissue hypoxia and elevating the susceptibility to multiple organ failure (MOF), including the brain.<sup>7</sup> Due to its high metabolic rate and oxidative nature, the brain consumes approximately 20% of the basal oxygen budget, despite its

relatively small size representing just 2% of body weight, making it susceptible to hypoxaemic conditions.<sup>8,9</sup> Main clinical presentations of hypoxaemia-induced acute brain injury (ABI) include ICU delirium, neurocognitive and affective impairments such as altered memory, attention, concentration, agitation, confusion, disorientation and/or mental processing speed even after long periods following the development of lung injury (LI) and ARDS, encephalopathy, and poorly organized movements.<sup>6</sup> Radiologic structural types of brain injuries incorporate cerebral ischaemia, diffuse hypoxic-ischaemic injury, cerebral microbleeds (CMBs), and intraparenchymal haemorrhage.<sup>10</sup>

CMBs manifest as small-sized, hypodense lesions measuring up to 10 mm in size on magnetic resonance imaging (MRI) sequences sensitive to haemorrhage. While their etiologic link to chronic hypertension, cerebral amyloid angiopathy, and diffuse axonal injury is well established, recent observations suggest potential causality with less easily identifiable factors like sepsis and ARDS.<sup>11</sup> Although descriptions of multiple microhaemorrhages affecting various brain regions such as the cortex, deep and periventricular white matter, basal ganglia, and thalami were reported almost a decade ago in critically ill patients with ARDS who were receiving mechanical ventilation (MV), their potential pathophysiological relevance in the progression and prognosis of ARDS patients has become increasingly apparent during the Coronavirus disease 2019 (COVID-19) pandemic.<sup>12–14</sup>

The occurrence of CMBs in patients with LI/ARDS is highly probable, emphasizing the crucial role of MRI in diagnosing this condition to prevent misdiagnoses like haemorrhagic encephalitis linked to underlying conditions such as sepsis or severe acute respiratory syndrome *coronavirus* 2 (SARS-CoV-2) infection. Taking into account that CMBs may be independently associated with short and long-term cognitive dysfunction, recognizing this entity is imperative for optimizing patient care, especially concerning long-term prognosis and preventive strategies.<sup>6,15,16</sup> Moreover, understanding the prevalence of CMBs in ARDS, both in the context of COVID-19 and non-COVID-19 cases, is crucial for elucidating the underlying pathophysiology and guiding clinical management. To our knowledge, this is the first scoping review to comprehensively evaluate the literature on CMBs in ARDS, with a focus on hypothesized mechanisms, radiological patterns, and clinical implications. Specifically, we aim to assess the impact of MV, identify associated risk factors and comorbidities, describe relevant clinical and radiological findings, and investigate potential long-term consequences such as cognitive dysfunction. Through this, we seek to highlight consistent imaging features, delineate current gaps in mechanistic understanding and shed light on the complex, bidirectional interplay between respiratory and neurological manifestations in critical illness.

## Methodology

The PRISMA Extension for Scoping Reviews were followed in this paper ([Supplementary Table 1](#)).<sup>17</sup> The review protocol was not pre-registered in the International Prospective Register of Systematic Reviews PROSPERO as the registry does not currently accept scoping reviews. To maintain methodological rigor and transparency, we based our approach on the framework proposed by Arksey and O'Malley, later refined by Levac et al, and reported our findings according to the PRISMA-ScR guidelines.<sup>17–19</sup>

## Search Strategy

Two authors (SCZ and MZ) independently conducted the literature search between February 1 and March 31, 2025. We systematically searched PubMed and CENTRAL, and study registries (PROSPERO and Clinicaltrials.gov) to identify all relevant clinical studies on CMBs in patients with severe respiratory failure and LI/ARDS, using a comprehensive search phrase that included terms such as “cerebral”, “brain”, “microbleeds”, “micro bleeds”, “respiratory”, “acute respiratory distress syndrome”, “ARDS”, “critical”, “intensive care”, “ICU” ([Supplementary Table 2](#)). Boolean operators (AND, OR) and truncation were used to refine and optimize the search strategy. Additionally, the reference lists of all included studies were screened to identify further relevant articles. We included studies involving adult human subjects, published in English, up to the current date.

## Inclusion and Exclusion Criteria

We included randomized controlled trials and observational studies (cohort, case-control, and cross-sectional studies) reporting data on the presence of CMBs in patients with severe respiratory failure and ARDS, whether mechanically

ventilated or not. Both peer-reviewed articles and preprints were eligible for inclusion, while case reports and case series involving fewer than five patients were excluded. Case reports and animal studies were excluded; therefore, studies reporting genetic associations (typically presented as case reports) and histopathological investigations (primarily based on animal models) were not part of the present synthesis. Additionally, studies with potential patient overlap (eg, from the same hospital or medical center within the same or overlapping time periods) were not considered.

## Data Extraction

Titles and abstracts of studies identified through the search strategy, as well as those from additional sources, were independently screened by multiple authors for eligibility based on predefined inclusion criteria. Data extraction was then performed independently by two reviewers (SCZ and MZ) using a structured, standardized form. Discrepancies in study selection or data extraction were resolved through discussion or, if necessary, by consulting a third author. Extracted data included publication details (authors, year), study design, geographic location, patient characteristics, pathophysiological hypotheses, use and duration of MV, clinical parameters, risk factors, radiologic findings, long-term outcomes, and study conclusions.

## Outcomes of Interest

The primary outcome was to assess the proposed pathophysiological mechanisms underlying the development of CMBs in patients with severe respiratory failure or ARDS, regardless of MV status. Secondary outcomes included the use and duration of MV in critically ill patients with CMBs, associated risk factors, preexisting comorbidities, clinical symptoms, and the anatomical distribution of CMBs. Additionally, we examined the impact of CMBs on long-term neurological function and their potential association with overall clinical severity.

## Data Synthesis

Extracted information was compiled into evidence tables to enable structured comparison across studies. Two reviewers (SCZ and MZ) independently analyzed the data, focusing on recurrent concepts and patterns across the included studies. Findings were grouped into thematic domains, including pathophysiological hypotheses, use and duration of mechanical ventilation, indications for brain MRI, anatomical distribution of cerebral microbleeds, comorbidities, risk factors, and post-ICU characteristics. These categories were refined through team discussion until consensus was achieved. The final synthesis was presented narratively, supported by evidence tables, to provide a transparent overview of both the breadth and depth of the existing literature ([Supplementary Table 3](#)).

## Results

### Search Results

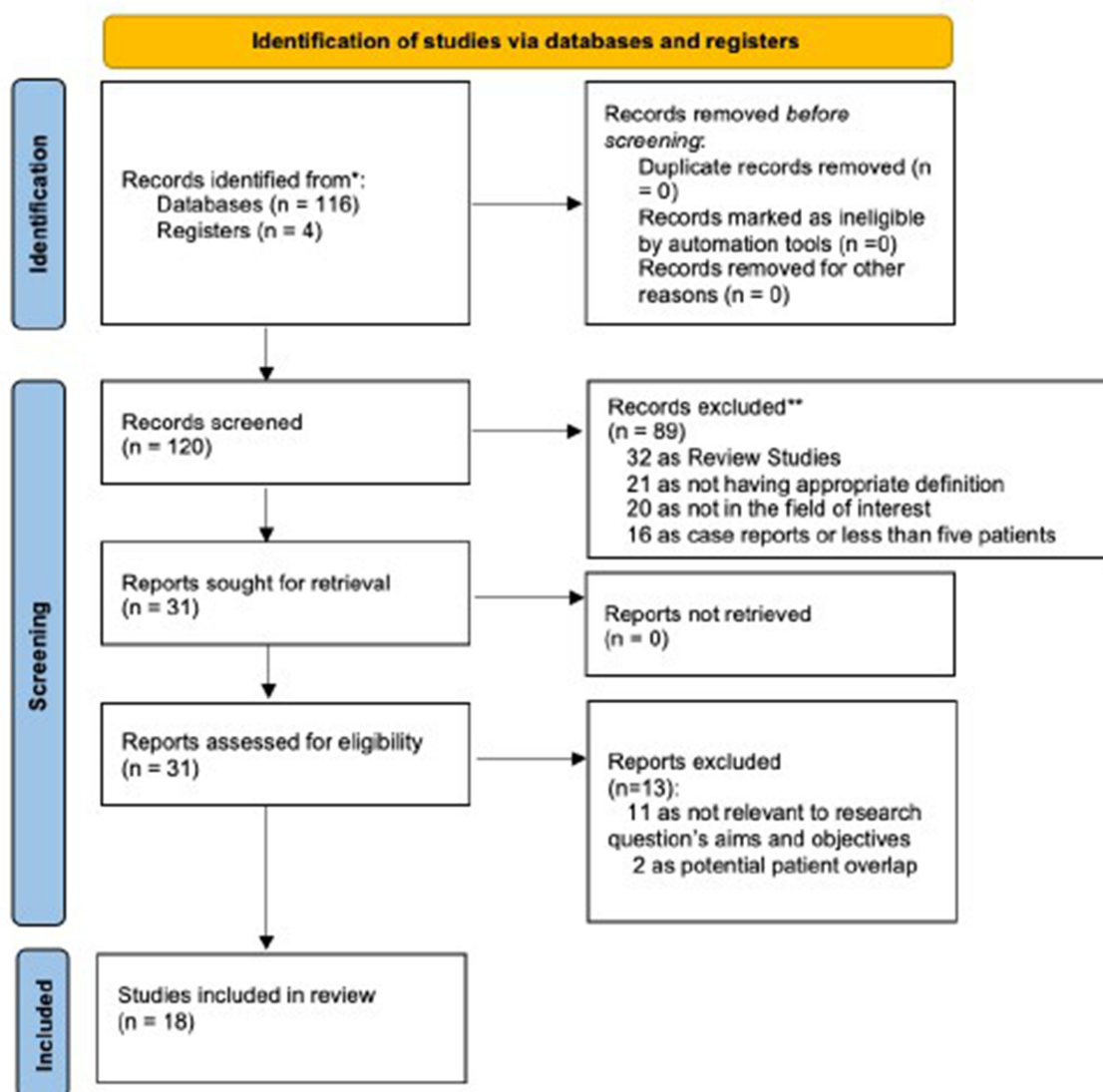
The preliminary database search yielded 120 studies. Each study was screened based on its title and abstract, and no duplicates were identified. A total of 31 publications met the initial criteria and were reviewed in full text, while 89 records were excluded based on title and abstract in accordance with the predefined inclusion and exclusion criteria. An additional 13 studies were excluded due to a lack of relevance to the research question's aims and objectives or because of potential patient population overlap. Ultimately, 18 studies were included in this review. The flow diagram of the search strategy is presented in [Figure 1](#).

### Characteristics of Included Studies

The included studies were published between 2017 and 2024.<sup>13,20</sup> Study types included eleven cohort studies, eight retrospectively<sup>21–28</sup> and three prospectively designed,<sup>20,29,30</sup> six retrospective case series with more than five patients per study,<sup>13,31–35</sup> and one retrospective cross-sectional study.<sup>36</sup>

The sample size of the studied population ranged from 9 to 214 patients.<sup>20,31</sup> Due to neurological complications, a subset of patients diagnosed with LI/ARDS undergo brain MRIs. Details of each study are summarized in [Table 1](#).

## PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only



\*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

\*\*If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

**Figure 1** Flow chart of the study.

## Hypothesized Pathophysiological Mechanisms of CMBs

Four distinct pathophysiological hypotheses have emerged regarding CMBs. The majority of included articles (11/18) suggest that hypoxaemia and inflammation may cause endothelial injury and blood–brain barrier (BBB) dysfunction. This dysfunction could result in the extravasation of erythrocytes and the development of diffuse CMBs, which are a phenotype typical of small vessel disease.<sup>13,20,22–26,31,32,34,35</sup> In COVID-19 patients, Agarwal et al further hypothesized that cerebral hypoperfusion enables the virus to interact with ACE2 receptors, which are widely expressed in endothelial

**Table 1** Main Characteristics and Findings of the Included Studies

| Study                             | Country | Type of Study                   | Study Population                                                  | Indications for Brain Imaging                                                                                                      | Anatomic Location                                                                                                           | Risk Factors and Comorbidities (Statistically Significant $p<0.05$ )                                                                                                                                       | MV in Patients with CMBs n/N (%)          | Days of MV, Median (IQR)                   | Main Findings                                                                                                                                                                                                                                           |
|-----------------------------------|---------|---------------------------------|-------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|--------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Fanou et al 2017 <sup>13</sup>    | Canada  | Retrospective case-series study | Patients with non-COVID respiratory failure admitted to the ICU   | Decreased level of consciousness, weakness, seizures, cognitive impairment, fever                                                  | Juxtacortical white matter and corpus callosum, internal capsule, or posterior fossa                                        | Thrombocytopenia, severe thrombocytopenia, prolonged PT, prolonged aPTT. Hypertension, haematologic malignancy, and nonmalignant haematologic disease. (potential factors; based on descriptive data only) | 11/12 (91.6%)                             | n.m.                                       | Uncertain cause of microbleeds, but hypoxaemia is possible.                                                                                                                                                                                             |
| Gedansky et al 2023 <sup>21</sup> | USA     | Retrospective cohort study      | Non-COVID patients with ARDS admitted to the ICU                  | Encephalopathy, evaluation of stroke, seizures                                                                                     | Lobar; deep, infratentorial, corpus callosum                                                                                | Hyperlipidaemia, patients with CMBs received rescue therapies more frequently                                                                                                                              | n.m.                                      | CMBs: 27.5 (14–42.5); No CMBs: 18 (10–28)  | CMBs may be related to ARDS or its treatment.                                                                                                                                                                                                           |
| Ollila et al 2024 <sup>20</sup>   | Finland | Prospective cohort study        | Severe COVID-19 patients without major neurological complications | Investigation of MRI findings 6 months after hospital discharge, or, concerning the home-isolated patients, a positive test result | Infratentorial, including splenium, cerebellum, and brainstem, and lobar (frontal, temporal, parietal, and occipital lobes) | Older age, higher CCI, higher level of plasma NfL, and severity of respiratory failure, higher supplementary oxygen days, highest ALT, delirium diagnosis                                                  | 20/27 ICU-treated COVID-19 patients (74%) | CMBs: 15.5 (12.8–28.3); No CMBs: 10 (7–13) | 39% of ICU-treated COVID-19 patients presented with CMBs six months after acute COVID-19. CMBs were related to severe hypoxaemia, with a predilection for the splenium. Age and length of supplementary oxygen were independently associated with CMBs. |

(Continued)

Table 1 (Continued).

| Study                            | Country | Type of Study                       | Study Population                                         | Indications for Brain Imaging                                                                                                                                      | Anatomic Location                                                                                        | Risk Factors and Comorbidities (Statistically Significant $p < 0.05$ )                                                                                                                                                                                                   | MV in Patients with CMBs n/N (%) | Days of MV, Median (IQR)                                                                                                               | Main Findings                                                                                                                                                                                                                                                                                         |
|----------------------------------|---------|-------------------------------------|----------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Helms et al 2020 <sup>29</sup>   | France  | Prospective cohort study            | Patients with ARDS due to SARS-CoV-2 admitted to the ICU | Severe and persistent delirium (> 3 days during ICU stay) and/or abnormal neurological examination (acute attention, awareness, cognition disturbances, agitation) | Infra- and supratentorial white matter microhaemorrhages                                                 | n.m.                                                                                                                                                                                                                                                                     | n.m.                             | n.m. for patients with CMBs                                                                                                            | SARS-CoV-2 infection may be associated with delirium and/or neurological symptoms, potentially due to a systemic inflammatory reaction.                                                                                                                                                               |
| Agarwal et al 2020 <sup>22</sup> | USA     | Retrospective cohort study          | COVID-19 adult patients received an MRI                  | Encephalopathy, focal weakness, aphasia, apneic episodes, and seizures                                                                                             | Diffuse, lobar, pons/ cerebellum, corpus callosum, splenium, subcortical white matter, deep white matter | Thrombocytopaenic with lower nadir platelet counts, higher peak D-dimer, and higher peak international normalized ratio values (patients with cerebral leukoencephalopathy and/or cerebral microbleeds); though the 2 groups were not differences in other comorbidities | 33/35 (94.2%)                    | Leukoencephalopathy and/or CMBs: 34.6 prolonged (mean). Other MRI Brain Findings (Without Leukoencephalopathy and/or CMBs): 9.1 (mean) | Leukoencephalopathy and/or CMBs are associated with severe hypoxaemia, prolonged MV, increased mortality, and worse functional outcome in patients with COVID-19                                                                                                                                      |
| Chougar et al 2020 <sup>36</sup> | France  | Retrospective cross-sectional study | COVID-19 patients with acute neurological manifestations | Impaired consciousness not explained by therapy, focal neurological deficit, seizures                                                                              | Corpus callosum                                                                                          | Increased partial thromboplastin time (potential factor; statistical significance not established)                                                                                                                                                                       | n.m.                             | n.m.                                                                                                                                   | ICU patients had a greater number of multiple microhaemorrhages than non-ICU patients involving the corpus callosum in 5 patients. Potential pathogenetic mechanisms include ECMO management, anticoagulation overdose, and microvascular damage. A possible implication of COVID-19 remains unclear. |

|                                         |             |                                 |                                                        |                                                                                                               |                                                                                                                  |                                                                                                                                                                                                                                      |                                                                                                  |                                                                                                                                                                                                   |                                                                                                                                                                                                           |
|-----------------------------------------|-------------|---------------------------------|--------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Fitsiori et al 2020 <sup>31</sup>       | Switzerland | Retrospective case series study | COVID-19 patients with ARDS admitted to the ICU        | Impaired consciousness or important agitation or confusion                                                    | Corpus callosum, internal capsule, cerebellum, subcortical regions                                               | n.m.                                                                                                                                                                                                                                 | 9/9 (100%)                                                                                       | Mean: 15,7 (manually calculated); Median: 14 (8–27)                                                                                                                                               | CMBs in COVID-19 may occur in atypical locations. Potential pathogenetic mechanisms include direct damage of SARS-CoV-2 to the endothelium of the brain vessels, severe hypoxaemia, and prolonged MV.     |
| Klironomos et al 2020 <sup>23</sup>     | Sweden      | Retrospective cohort study      | Hospitalized COVID-19 patients undergoing neuroimaging | Prolonged consciousness impairment after extubation, follow-up                                                | Splenium, corpus callosum, juxtacortical U-fibers (SWI abnormalities)                                            | n.m.                                                                                                                                                                                                                                 | n.m.                                                                                             | n.m.                                                                                                                                                                                              | Plausible pathophysiological mechanisms may include hypoxia, ischaemia, stasis (with deoxyhaemoglobin-rich blood), thrombosis, haemorrhages, inflammation, endothelial injury, or a combination of these. |
| Jegatheeswaran et al 2022 <sup>24</sup> | Canada      | Retrospective cohort study      | COVID-19 patients undergoing neuroimaging              | Confusion/delirium, altered LOC, focal neurological deficit                                                   | Juxtacortical white matter, corpus callosum, one patient with cortical superficial siderosis (SWI abnormalities) | The most common comorbidities for all patients in the study were hypertension (67.0%), dyslipidemia (46.6%), and type II diabetes (36.9%), but without separate mention for the CMB group (statistical significance not established) | 3/3 patients with CMBs (100%) [4 SWI abnormalities (3: CMBs, 1: cortical superficial siderosis)] | Prolonged (>20 days)                                                                                                                                                                              | CMBs are associated with prolonged MV. Hypoxaemia could represent one potential pathogenetic mechanism.                                                                                                   |
| Lersy et al 2021 <sup>25</sup>          | France      | Retrospective cohort study      | Patients with ARDS due to COVID-19 admitted to the ICU | Impaired consciousness, confusion, agitation, seizures, and clinical signs of corticospinal tract involvement | Preferential frontal lobe involvement, corpus callosum, internal capsule, and middle cerebellar peduncles        | Higher increase of the D-dimers, higher creatinine level, higher urea levels, and more haemodialysis, increased use of ECMO, and more extended pulmonary disease. More severe respiratory failure, more severe ARDS                  | n.m.                                                                                             | Population of COVID-19 patients with extensive white matter microhaemorrhages: 24 (19–25) – prolonged. Population of COVID-19 patients without extensive white matter microhaemorrhages: 8 (4–14) | The primary mechanism leading to cerebral microbleeds associated with critical illness appears to be dysfunction of the BBB due to hypoxaemia and elevated levels of uraemic toxins.                      |

(Continued)

Table 1 (Continued).

| Study                             | Country | Type of Study                   | Study Population                                | Indications for Brain Imaging                                                                                                                                         | Anatomic Location                                                                                                                            | Risk Factors and Comorbidities (Statistically Significant $p<0.05$ )                                                                                                                                                                                                  | MV in Patients with CMBs n/N (%) | Days of MV, Median (IQR)                                                                                                | Main Findings                                                                                                                                                                                                               |
|-----------------------------------|---------|---------------------------------|-------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|-------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Huang et al 2024 <sup>26</sup>    | USA     | Retrospective cohort study      | Patients with non-COVID ARDS received MRI       | Encephalopathy, stroke evaluation, neurological manifestations (seizures, coma, focal weakness), post-cardiac arrest, evaluation of infection, evaluation of neoplasm | Deep and lobar structures (including the genu and splenium of the corpus callosum), cerebellum                                               | Not specifically mentioned for CMBs. For all patients with cerebral haemorrhagic complications: Hyperlipidaemia, significantly greater use of rescue therapies, higher frequency of septic shock, higher admission glucose levels, more severe lowest platelet count. | n.m.                             | Not specifically mentioned for CMBs. For all patients with cerebral haemorrhagic complications: MV 23 (11–41) prolonged | Patients with cerebral haemorrhage had a notably higher occurrence of ARDS rescue therapies, such as prone positioning, inhaled vasodilation, and recruitment maneuvers, indicating the severity of oxygenation impairment. |
| Thurnher et al 2021 <sup>32</sup> | Austria | Retrospective case series study | Mechanically ventilated critically ill patients | n.m.                                                                                                                                                                  | Subcortical white matter, white-gray matter interface, infratentorial, corpus callosum, internal capsule, midbrain/ pons (SWI abnormalities) | n.m.                                                                                                                                                                                                                                                                  | 14/14 (100%)                     | n.m.                                                                                                                    | The pathophysiology of CMBs development appears to be associated with MV, prolonged respiratory failure, and hypoxaemia.                                                                                                    |
| Conklin et al 2021 <sup>33</sup>  | USA     | Retrospective case series study | Patients with COVID-19-ARDS treated in the ICU  | Coma, unresponsiveness, focal neurologic deficits                                                                                                                     | Corpus callosum, subcortical and deep white matter, brainstem, cerebellum, thalamus (SWI abnormalities)                                      | n.m.                                                                                                                                                                                                                                                                  | 11/11 (100%)                     | n.m.                                                                                                                    | Individuals suffering from severe COVID-19 face the potential risk of developing multiple microvascular haemorrhagic and ischaemic lesions in the subcortical and deep white matter of the brain.                           |

|                                      |             |                                 |                                                   |                                                                                             |                                                                                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                           |                                  |           |                                                                                                                                                                                                                                                                                                                         |
|--------------------------------------|-------------|---------------------------------|---------------------------------------------------|---------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|-----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Büttner et al 2021 <sup>27</sup>     | Germany     | Retrospective cohort study      | Hospitalized COVID-19 patients                    | Focal neurological deficits, seizures, reduced consciousness, psychiatric symptoms          | Superficial and deep white matter                                                                                                    | Risk factors were mentioned in general, but without separate mention for the CMB group (statistical significance not established)                                                                                                                                                                                                                                                                         | 7/7 (and/or ECMO support) (100%) | n.m.      | Microbleeds distributed throughout the white matter, encompassing both superficial and deep regions. This pattern could be attributed to therapeutic anticoagulation, possibly compounded by elements of critical illness or ARDS.                                                                                      |
| Klinkhammer et al 2023 <sup>30</sup> | Netherlands | Prospective cohort study        | ICU and general ward (non-ICU) COVID-19 survivors | Investigation of MRI findings 6 months after ICU discharge                                  | Corpus callosum                                                                                                                      | Not specifically mentioned for CMBs                                                                                                                                                                                                                                                                                                                                                                       | 60/60 (100%)                     | n.m.      | ICU survivors of COVID-19 exhibited a greater prevalence and frequency of microbleeds compared to non-ICU patients. These microbleeds were more frequently found in the corpus callosum. Despite the increased incidence of microbleeds among ICU survivors, cognitive dysfunction was equally observed in both groups. |
| Dixon et al 2020 <sup>34</sup>       | UK          | Retrospective case series study | COVID-19 patients with ARDS                       | Altered mental state, weakness, seizures, tremor, abnormal brainstem pattern of ventilation | Corpus callosum, juxtacortical and subcortical white matter of both cerebral hemispheres (parietal lobes, cerebellum, and brainstem) | Antithrombotic therapy (10/10), mildly prolonged PT (5/10), AKI (90%).<br>Hypertension (5/10), diabetes (4/10), obesity (2/10), hyperlipidaemia (2/10). All patients had episodes of severe hypoxia, hypercapnia, and acidosis. All patients had high D-dimers and anaemia. 7/10 received haemodialysis or haemofiltration. 9/10 had high fibrinogen. (potential factors; based on descriptive data only) | 10/10 (100%)                     | 25 (5–43) | COVID-19-associated CMBs likely reflect hypoxia and critical illness rather than a unique feature of SARS-CoV-2, with endothelial dysfunction and blood–brain barrier breakdown as key contributors.                                                                                                                    |

(Continued)

**Table 1** (Continued).

| Study                              | Country | Type of Study                   | Study Population                                        | Indications for Brain Imaging                                               | Anatomic Location                                                                 | Risk Factors and Comorbidities (Statistically Significant $p < 0.05$ )                                                    | MV in Patients with CMBs n/N (%) | Days of MV, Median (IQR)                                                                    | Main Findings                                                                                   |
|------------------------------------|---------|---------------------------------|---------------------------------------------------------|-----------------------------------------------------------------------------|-----------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------|----------------------------------|---------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| Kremer et al 2020 <sup>28</sup>    | France  | Retrospective cohort study      | Severe COVID-19 patients with neurologic manifestations | Alteration of consciousness, pathological wakefulness, confusion, agitation | Subcortical white matter, corpus callosum, internal capsule, cerebellar peduncles | Not specifically mentioned for CMBs. For all patients with haemorrhagic lesions: Leukocytosis, anaemia, renal dysfunction | n.m.                             | n.m.                                                                                        | The pathophysiology of CMBs remains uncertain and will require further studies.                 |
| Radmanesh et al 2020 <sup>35</sup> | USA     | Retrospective case series study | Critically ill patients with COVID-19                   | Persistently diminished mental status                                       | Juxtacortical white matter and/or corpus callosum, particularly the splenium      | Anticoagulation (potential factor; based on descriptive data only)                                                        | 7/7 (100%)                       | Mean duration 26.5 days (for all patients, not mentioned separately for patients with CMBs) | CMBs are potentially linked to hypoxia and/or small vessel vasculitis as a contributing factor. |

**Abbreviations:** AKI, acute kidney injury; aPTT, activated partial thromboplastin time; ARDS, acute respiratory distress syndrome; BBB, blood brain barrier; CCI, Charlson comorbidity index; CMB, cerebral microbleed; COVID-19, Coronavirus Disease 19; ICU, intensive care unit; PT, ECMO, extracorporeal membrane oxygenation; LOC, level of consciousness; MRI, magnetic resonance imaging; MV, mechanical ventilation; NFL, neurofilament light chain; nm, not mentioned; PT, prothrombin time; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SWI, Susceptibility-weighted imaging.

cells. This damages the endothelium and increases the likelihood of microhaemorrhages by making the watershed zone vulnerable.<sup>22</sup> Moreover, a different theory concerning microangiopathy with diffuse microthrombi may provide insight into the occurrence of CMBs.<sup>22,25,31,34,36</sup> Another hypothesis emphasized the impact of renal insufficiency. Chronic kidney disease and haemodialysis are associated with a higher prevalence of CMBs, likely due to physiological mechanisms such as compromised BBB resulting from elevated concentrations of uraemic toxins.<sup>25</sup>

## Mechanical Ventilation

Among the included studies, fourteen reported on the use of MV in critically ill patients with respiratory failure. Specifically, in patients with COVID-19-associated respiratory failure, 74–100% underwent MV.<sup>13,20–22,24–27,30–35</sup> Notably, the study by Ollila et al reported the lowest MV rate at 74% (manually calculated).<sup>20</sup> Excluding this study, the remaining data indicate MV was administered in 94.2–100% of patients with CMBs.<sup>22,24,27,30,31,33–35</sup> In cases of non-COVID-related respiratory failure, 91.6–100% of patients received MV.<sup>13,32</sup>

In patients with COVID-19-associated respiratory failure, the duration of MV ranged from 5 to 43 days.<sup>20,22,25,31,34,35</sup> Reported median durations varied between 14 and 25 days. In comparison, for non-COVID-related ARDS, Gedansky et al (2023) reported MV durations ranging from 14 to 42.5 days.<sup>21</sup> Compared to patients without CMBs, those with CMBs experienced a significantly longer duration of MV.<sup>20–22,25</sup>

## Symptom-Based Indications for Brain MRI

Fifteen out of the 18 included studies described the clinical symptoms or neurological signs that prompted the decision to perform brain imaging. Indications for brain imaging include decreased level of consciousness, weakness (unilateral, bilateral, or generalized), seizures, cognitive impairment (eg, delirium, encephalopathy, confusion, agitation, or delayed recovery of consciousness), persistent fever, and coma despite sedation withdrawal.<sup>13,21–29,31,33–36</sup> None of the symptoms could be explained by metabolic disturbances or withdrawal syndromes. In two studies, neurologic status appeared to be more severe when CMBs were extensive.<sup>25,27</sup>

## Anatomical Distributions of CMBs

The 18 studies included in the present work all provided information on the brain regions affected by CMBs. The corpus callosum<sup>13,21–26,28,30–36</sup> and juxtacortical white matter<sup>13,21,23,24,28,33–35</sup> were the regions of the brain most commonly impacted. CMBs have also been observed in infratentorial areas, including the splenium,<sup>20,22,23,26,34,35</sup> cerebellum,<sup>20,22,26,31,33,34</sup> and brainstem,<sup>20,33,34</sup> as well as lobar regions such as the frontal, temporal, parietal, and occipital lobes.<sup>20–22,25,26,34</sup> In addition, microhaemorrhages appeared in subcortical and deep white matter regions,<sup>21,22,27–29,31–34</sup> along with specific areas like the internal capsule,<sup>13,25,28,31,32</sup> midbrain/pons,<sup>22,32</sup> and thalamus.<sup>33</sup>

The corpus callosum has been found to be affected in both COVID-19-related and non-COVID ARDS.<sup>13,20–24,31–33,35,36</sup> Moreover, brain imaging results for non-COVID ARDS patients have shown findings impacting both deep and lobar brain structures.<sup>21,26,32</sup> The distribution of CMBs in COVID-19 ARDS is notably diverse, with localization in different specific areas, including the infratentorial (such as the splenium, cerebellum, and brainstem) and lobar regions (frontal, temporal, parietal, and occipital lobes). Additionally, there is involvement of cortical, subcortical, and cerebellar areas, as well as the corpus callosum.<sup>23–25,28,30,32–35</sup>

## Comorbidities

Hypertension and dyslipidaemia were the most commonly reported comorbidities, followed by diabetes and both malignant and non-malignant haematologic diseases.<sup>13,20–22,24,26,34</sup> Agarwal et al (2020)<sup>22</sup> reported no discernible difference in the prevalence of comorbidities between COVID-19 patients with and without CMBs. Similarly, Huang et al (2023)<sup>26</sup> found no significant differences in comorbidities among patients with CMBs during the non-COVID era.

## Risk Factors for CMBs

The overview of risk factors for CMBs includes thrombocytopaenia, especially severe thrombocytopaenia observed in a subgroup of patients.<sup>13,22,26</sup> Individuals with CMBs tended to have prolonged prothrombin time (PT) and activated

partial thromboplastin time (aPTT), higher peak D-dimer levels, and elevated peak international normalized ratio (INR) values.<sup>13,22,25,34,36</sup> Four studies reported a significant association between the presence of CMBs and elevated levels of neurofilament light chain (NfL), increased serum creatinine (renal impairment and a higher rate of dialysis during ICU stay), and elevated serum glucose concentrations.<sup>20,25,26,34</sup> Furthermore, characteristics linked to the occurrence of CMBs were increasing age, a greater Charlson Comorbidity Index (CCI), and the severity of respiratory failure.<sup>20,22,25,31,34</sup> CMBs were more likely to have moderate and severe ARDS syndrome scores.<sup>22,25,31</sup>

## Post-ICU Characteristics of Patients

In the research conducted by Fanou et al (2017) in patients with non-COVID-associated respiratory failure, cognitive abnormalities (such as difficulty concentrating and short-term memory impairment) were observed in 5 out of 7 survivors.<sup>13</sup> Similarly, Agarwal et al (2020) highlighted that the patients in the CMBs group had worse functional status upon discharge compared to those without CMBs.<sup>22</sup> In contrast, Thurnher et al (2021) reported no significant neurological consequences in survivors, with 50% discharged from the ICU.<sup>32</sup> Consistently, Klinkhammer et al (2023) found that the number of CMBs was not predictive of cognitive impairment at the time of discharge.<sup>30</sup>

## Discussion

In this scoping review, we included 18 observational studies with sample sizes ranging from 9 to 214 patients. CMBs were most commonly observed in the corpus callosum and juxtacortical white matter. Most patients had experience prolonged MV. Risk factors for the development of CMBs included greater disease severity, coagulation abnormalities and renal dysfunction. The underlying pathophysiologic mechanisms likely involve hypoxaemia, inflammation, micro-angiopathy and BBB dysfunction.

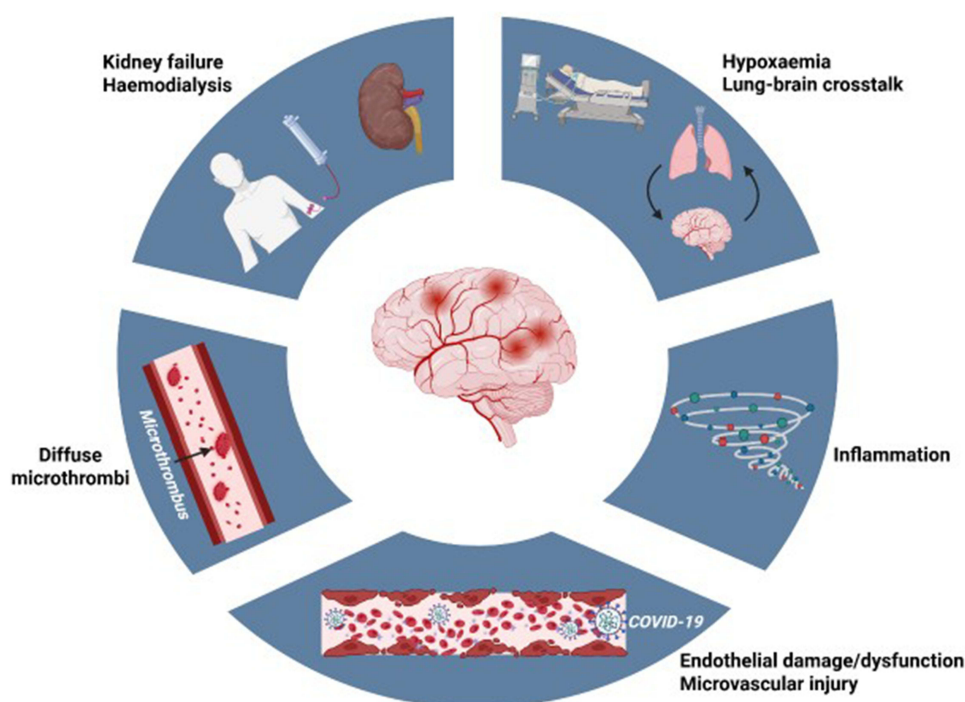
CMBs, also termed cerebral micro-hemorrhages, are identified as small hypointense areas on susceptibility-weighted (SW) MRI, ranging in size from up to 5 mm to 10 mm, and histopathologically represent focal aggregations of haemosiderin-containing macrophages.<sup>37,38</sup> Compromised small vessel integrity, such as that seen in hypertensive vasculopathy or cerebral amyloid angiopathy, is often associated with their development. Patients with Alzheimer's disease (AD) dementia and those who have suffered from both ischaemic and haemorrhagic strokes are more likely to exhibit microbleeds. However, they are also detected in asymptomatic individuals, and their prevalence tends to rise with age, particularly among carriers of the apolipoprotein (APOE)  $\epsilon 4$  allele.<sup>39</sup> Furthermore, during autopsies of individuals who suffered from high-altitude cerebral oedema, microhaemorrhages have been identified in the corpus callosum.<sup>40</sup> In recent years, CMBs have been reported increasingly in critically ill patients who require MV and/or extracorporeal membrane oxygenation (ECMO),<sup>13</sup> frequently impacting the juxtacortical white matter and corpus callosum. Most notably, patients with respiratory failure due to COVID-19 have recently exhibited this pattern of microbleeds.<sup>41</sup> To date, no reported evidence suggests that COVID-19 vaccination is associated with CMBs in ARDS, though this topic warrants further research.

From a mechanistic perspective, increasing evidence supports a significant role for cerebral microvascular injury in the development of CMBs in patients with severe respiratory failure. Prolonged hypoxaemia may induce endothelial dysfunction through oxidative stress and impaired autoregulation, while concomitant hypercapnia can lead to cerebral vasodilation and increased capillary permeability.<sup>35</sup> These processes may facilitate BBB disruption and erythrocyte extravasation into the perivascular space.<sup>13,27,42–45</sup> In addition, systemic inflammation and thromboinflammatory activation, characteristic of ARDS, promote microthrombi formation and endothelial damage within cerebral small vessels.<sup>26,46,47–</sup> In COVID-19, these mechanisms may be further amplified by virus-related endothelial injury and dysregulated immune responses, contributing to diffuse microangiopathy.<sup>46,48</sup> Emerging therapeutic approaches targeting endothelial injury and inflammation, including nanomedicine-based strategies, have shown promise in preclinical ARDS models and warrant exploration in the context of microvascular injury and CMBs.<sup>48,49</sup>

Additional disease conditions known to influence CMB prevalence may act as potential confounders in ARDS-related presentations. Hypertension and cerebral amyloid angiopathy have been identified as contributors to CMBs, with hypertensive vasculopathy often linked to deep or infratentorial microbleeds and amyloid pathology to lobar microbleeds.<sup>50</sup> Chronic kidney disease and haemodialysis have also been associated with increased prevalence of

CMBs, likely due to uraemic toxins and endothelial dysfunction.<sup>51</sup> These comorbidities may independently modulate the risk, distribution and severity of CMBs in patients with severe respiratory failure.

Despite that haemorrhagic complications are frequently documented in patients with LI/ARDS, the precise pathogenic mechanism underlying their occurrence remains elusive. As mentioned above, one hypothesis suggests that hypoxaemia and inflammation may contribute to endothelial injury and BBB dysfunction, potentially leading to the extravasation of erythrocytes and subsequent development of diffuse CMBs—a phenotype characteristic of small vessel disease.<sup>13,26</sup> In COVID-19 patients, it is hypothesized that reduced blood flow in cerebral microvessels allows the virus to interact with ACE2 receptors on capillary endothelium, potentially damaging the endothelial and facilitating viral access to the brain, leading to neuronal damage and dysfunction of the endothelial integrity within cerebral capillaries increasing the risk of cerebral haemorrhage.<sup>52</sup> The hypothesis of microvascular injury is further supported by the study of Shoskes et al (2022), which compared radiologic findings in patients with non-COVID and COVID-19-associated ARDS. **Figure 2** represents a simplified schematic illustration of the pathophysiological mechanisms involved in the development of CMBs in patients with severe respiratory failure and ARDS. Haemorrhagic leukoencephalopathy, defined as leukoencephalopathy combined with CMBs, was observed in 15% of patients with SARS-CoV-2 infection, while it was absent in those with non-COVID ARDS. Notably, cerebrospinal fluid (CSF) analysis in affected COVID-19 patients revealed no signs of inflammation. Based on these findings, the authors proposed that acute haemorrhagic encephalopathy in COVID-19 may be associated with microvascular injury rather than inflammatory mechanisms. However, previous cases of acute haemorrhagic encephalopathy related to infectious agents other than COVID-19—as well as studies involving SARS-CoV-2 patients—highlight a strong correlation between inflammatory and immune-mediated mechanisms and the pathophysiology of the condition.<sup>46,53,54</sup> Moreover, a further hypothesis regarding microangiopathy with diffuse microthrombi may provide insight into the widespread occurrence of brain microhaemorrhages.<sup>25</sup> Another speculation highlights the influence of kidney failure, which is notably more pronounced in patients with CMBs. Indeed, chronic kidney disease and haemodialysis are recognized factors associated with an elevated incidence of CMBs, likely due to physiological mechanisms such as impaired permeability of the BBB resulting from elevated concentrations of



**Figure 2** Simplified schematic representation of the pathophysiological mechanisms involved in the development of CMBs in patients with severe respiratory failure and ARDS.

**Abbreviations:** ARDS, Acute respiratory distress syndrome; CMBs, Cerebral microbleeds.

uraemic toxins.<sup>25</sup> In the authors' opinion, and considering the perivascular lesions described by Thurnher et al (2021),<sup>32</sup> the predominance of CMBs in patients with COVID-19, and the endotheliitis-centered thromboinflammatory response characteristic of SARS-CoV-2—which involves inflammatory and toxic cascades, thromboinflammation, and systemic microangiopathy<sup>55</sup>—endotheliitis may represent a central pathogenetic mechanism in the development of CMBs. This may align with the proposed pathophysiology of CMBs observed in septic patients without respiratory failure<sup>42</sup> and is further supported by the study of Ollila et al (2023), which reported the presence of CMBs in 17.4% of home-isolated COVID-19 patients,<sup>20</sup> a population with evidently less severe hypoxaemia—suggesting that mechanisms beyond respiratory failure may contribute to the development of CMBs. This hypothesis may also help explain why the majority of patients with CMBs were individuals with COVID-19. However, these findings likely reflect expected features of patients with severe respiratory failure and therefore represent associations rather than direct mechanistic insights.

In our study, the most commonly affected brain regions included the juxtacortical white matter and corpus callosum, particularly the splenium. Other locations where microbleeds were observed encompassed infratentorial areas such as the cerebellum and brainstem, as well as lobar regions including the frontal, temporal, parietal, and occipital lobes. Additionally, microhaemorrhages were found in subcortical and deep white matter regions, along with specific areas like the internal capsule, midbrain/pons, and thalamus, highlighting the diverse distribution of these lesions in the brain. Indeed, the corpus callosum has been identified as an affected region in both COVID-19-related and non-COVID ARDS cases based on the brain imaging findings from the studies provided.<sup>13,21–26,28,30–36</sup> Moreover, non-COVID ARDS patients undergoing brain imaging have also exhibited findings affecting deep and lobar brain structures.<sup>21,26,32</sup> In COVID-19 ARDS, the distribution of CMBs shows a greater diversity localizing in various specific locations such as the infratentorial regions (including the splenium, cerebellum, and brainstem) and lobar regions (frontal, temporal, parietal, occipital lobes), along with involvement of cortical, subcortical, and cerebellar areas, as well as the corpus callosum.<sup>24,25,28,30,32–35</sup> A plausible explanation for these differences could be that non-COVID-19 respiratory failure is underrepresented in our study, while the majority of the included studies predominantly focus on COVID-19 LI/ARDS. However, a recent meta-analysis noted that these patients demonstrate fewer deep or lobular microbleeds, typically associated with hypertensive angiopathy and cerebral amyloid angiopathy. Instead, the study highlights a diverse pattern of cerebral haemorrhagic manifestations in these patients, including diffuse microhaemorrhages affecting deep cortical white matter structures such as the corpus callosum, brainstem, and cerebellum.<sup>43</sup> The predominant occurrence of corpus callosum involvement is often noted in patients with high-altitude lesions<sup>12</sup> and patients with anoxic brain injury,<sup>44</sup> suggesting potential shared pathogenetic mechanisms between these disorders.<sup>6</sup> Earlier hypotheses have suggested that the pathogenesis of callosal microbleeds in acquired brain injury is primarily linked to increased permeability resulting from the disruption of the BBB and hypoxic vasodilation.<sup>45,56–58</sup> Indeed, in contrast to the anterior cerebral arteries, which give rise to other pericallosal arteries, the posterior pericallosal arteries, originating from the posterior cerebral arteries, specifically supply blood to the splenium of the corpus callosum. Therefore, the vascular anatomy of the corpus callosum may contribute to the predilection for callosal microbleeds to occur in the splenium.<sup>59</sup> A further hypothesis regarding the predominant involvement of the corpus callosum in patients with COVID-19 is that this structure, particularly the splenium, contains a high density of cytokine and glutamate receptors. These receptors may render the corpus callosum especially susceptible to the hyperinflammatory state associated with COVID-19, thereby increasing its sensitivity to these factors.<sup>60,61</sup> Moreover, brain endothelial erythrophagocytosis, which could be triggered by infectious factors and is associated with oxidative stress in the brain endothelium, leads to the translocation of iron-rich red blood cells or their degradation products across the brain endothelium, a process that could explain the occurrence of microbleeds without disrupting the microvasculature, supporting the notion of pseudo-microbleeds.<sup>47,62</sup>

Brain imaging was performed in a range of clinical scenarios based on presenting symptoms. Indications included decreased level of consciousness, focal weakness, seizures, cognitive impairment, fever, and persistent coma following sedation withdrawal.<sup>13,21–29,31,33–36</sup> Additionally, investigations were conducted post-ICU discharge, specifically focusing on delirium accompanied by acute attention, awareness, and cognition disturbances, as well as agitation. Other indications included encephalopathy with focal weakness, aphasia, apneic episodes, and seizures, and cases of impaired consciousness not explained by therapy, along with focal neurological deficits and seizures.<sup>21–29,31,33–36</sup> Diagnostic brain assessments were also prompted by prolonged consciousness impairment after extubation, follow-up

for encephalopathy, and indications such as confusion, altered level of consciousness, and signs of corticospinal tract involvement.<sup>22,24–28,31,34,35</sup> Comparing the clinical findings of patients with CMBs at high altitude to those described in ARDS, there are notable similarities and differences. Both are characterized by symptoms like confusion, ataxia, headache, and coma, whereas patients with CMBs in the context of high-altitude also present with additional symptoms such as dyspraxia, fatigue, and incontinence.<sup>63</sup> These differences between the clinical findings of high-altitude patients and those in our study may be attributed to factors such as the high percentage of intubated and sedated patients in our study. Symptoms like dyspraxia (impaired motor planning) and incontinence might be challenging to recognize or report accurately in patients who are intubated and sedated, potentially leading to underestimation or misinterpretation of certain clinical features. Finally, regarding the impact of CMBs on long-term outcomes, the existing evidence in patients with severe respiratory failure is sparse. Data from community-dwelling populations show varying results. While certain studies propose that CMBs independently predict cognitive impairment, others suggest that this association weakens when adjusting for additional markers of vascular brain injury, like white matter hyperintensities and infarcts.<sup>64</sup>

Identified risk factors for CMBs included thrombocytopaenia, with severe cases observed in a subset of patients. Prolonged PT and aPTT were also commonly reported among individuals with CMBs. Additionally, advancing age, a higher CCI, and greater severity of respiratory failure were associated with the presence of CMBs. Patients with CMBs demonstrated lower nadir platelet counts, elevated peak D-dimer levels, and increased peak INR values.<sup>13,22,25,34,36</sup> Notably, patients with microhaemorrhages often had increased aPTT due to preventive anticoagulation therapy.<sup>36</sup> Indeed, coagulation disturbances observed in ARDS are widely recognized and are primarily ascribed to tissue factor (TF) exposure,<sup>65</sup> which activates coagulation pathways and impairs endogenous anticoagulant function. This cascade leads to uncontrolled intravascular coagulation, causing microvascular and endothelial damage, ultimately resulting in organ dysfunction.<sup>66,67</sup> Additionally, patients with kidney injury—regardless of whether they required haemodialysis—exhibited a higher incidence of CMBs. This association may partially reflect the contribution of uraemic-mediated mechanisms to the pathogenesis of CMBs.<sup>25,28,34</sup> Common comorbidities among patients with CMBs included hypertension, dyslipidaemia, and type II diabetes.<sup>13,21,24,26,34</sup>

Overall, the presence of CMBs and associated brain findings was linked to extended periods of MV in these patient populations.<sup>20–22,24,25,31,34,35</sup> However, it is challenging to determine definitively whether the presence of CMBs leads to a prolonged duration of MV or if prolonged MV results in a higher incidence of CMBs. The relationship between these factors requires further investigation and may be influenced by various patient-specific and clinical factors. Compared to patients without CMBs, those with CMBs experienced a significantly longer duration of MV.<sup>20–22,25</sup> Prolonged MV could be linked to numerous adverse events, including nosocomial infections, poor clinical outcomes, increased need for critical care interventions, and the development of post-intensive care syndrome.<sup>68–70</sup> However, most findings are derived from retrospective or observational designs with limited mechanistic detail. Thus, while these hypotheses remain plausible, they require validation in studies that integrate pathological, biochemical, or translational approaches. To date, there are no studies directly comparing the distribution patterns of CMBs across different types of respiratory support (HFNC, NPPV, IPPV) or according to mechanical ventilation parameters. However, prolonged MV and severe hypoxaemia and hypercapnia have been associated with increased risks of CMBs, suggesting that ventilatory factors may influence microvascular injury.

In patients with severe respiratory failure, the choice of respiratory support using nasal cannula, high-flow nasal cannula (HFNC), noninvasive positive pressure ventilation (NPPV), or invasive positive pressure ventilation (IPPV) depends on both the underlying disease and the severity of hypoxaemia.<sup>71</sup> Conversely, in the setting of ARDS, IPPV has historically been regarded as the standard of care. However, according to the JRS/JSICM/JSRCM-GL2021 guidelines, HFNC and NPPV are recommended as alternative options for initial management.<sup>72</sup> Protective MV, characterized by low tidal volume and application of positive end-expiratory pressure (PEEP), has been extensively documented to improve outcomes in patients with ARDS by mitigating lung strain and inflammation.<sup>2,6,73</sup> Nonetheless, it is crucial to recognize that implementing a protective ventilator strategy can potentially lead to self-inflicted lung injury and hypercapnia, which can cause cerebral vasodilation, elevated cerebral blood flow, and intracranial hypertension.<sup>74</sup> Furthermore, as previously noted, evidence suggests that BBB disruption due to endothelial injury—linked to hypoxaemia and inflammatory

cascades—may contribute to the pathogenesis of CMBs through erythrocyte extravasation.<sup>13,26</sup> Experimental studies have further shown that the combination of hypoxaemia and hypercapnia can enhance BBB permeability via complex molecular mechanisms, including the degradation of tight junction proteins by matrix metalloproteinases, whose production is triggered, among other factors, by elevated carbon dioxide levels.<sup>75</sup>

## Limitations

Limitations of this study include the heterogeneity in design, sample size, populations, and imaging indications, with several lacking detailed reporting of risk factors or neuroimaging protocols. This variability limits the robustness of our synthesis and weakens the strength of evidence regarding mechanisms and CMB distributions. Additionally, the majority of the studies analyzed focused on patients with COVID-19-related respiratory failure, which may limit the generalizability of findings to other populations with ARDS. Furthermore, this study did not investigate the primary cause of ARDS, which could potentially influence the occurrence of CMBs and introduce bias into the analysis. Another limitation of our study is the inclusion of studies referring to SWI microsusceptibility foci. Although these abnormalities are most commonly associated with microbleeds, other etiologies cannot be excluded. Moreover, by excluding case reports and animal studies, our review did not capture genetic or histopathological findings. This focus enhanced clinical relevance but limited mechanistic depth, which future reviews combining clinical and preclinical data could address. As this is a scoping review, a formal critical appraisal of individual studies was not performed. While study characteristics were summarized to provide context, the absence of a formal quality assessment may limit the interpretation of the evidence. Lastly, our search was limited to PubMed and CENTRAL, which may have excluded relevant studies in other databases and we did not include gray literature.

## Conclusion

Our study maps evidence on CMBs predominantly in the corpus callosum and juxtacortical white matter, in patients with respiratory failure, including both non-COVID ARDS and COVID-19-related cases. Their development is linked to compromised small vessel integrity, hypoxia, inflammation, and potential viral effects, aggravated by coagulation disturbances and BBB dysfunction. However, these remain largely hypothetical, as current studies are predominantly observational and provide associative rather than causal insights. The novelty of our work lies in synthesizing this heterogeneous literature and highlighting the consistent radiological patterns that emerge despite methodological variability. Recognizing these imaging patterns may support early identification of patients at risk and guide ICU management. While CMBs correlate with prolonged MV and disease severity, their impact on long-term outcomes remains uncertain. Future research should clarify causal mechanisms and optimize patient care.

## Language Editing Assistances

This manuscript has been edited for language issues using AI-assisted tools.

## Abbreviations

CMBs, cerebral microbleeds; ARDS, acute respiratory distress syndrome; MV, mechanical ventilation; BBB, blood–brain barrier; COVID-19, coronavirus disease 2019; ACE2, angiotensin-converting enzyme 2 receptors; ICU, Intensive Care Unit; MOF, multiple organ failure; ABI, acute brain injury; LI, lung injury; MRI, magnetic resonance imaging; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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Figure 2 is created with BioRender.com.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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The authors declare that they have no competing interests in this work.

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