Study Title

Re**L**at**I**onship **BE**tween implementation of evidence-based and suppo**R**tive ICU c**A**re and ou**T**comes of pat**I**ents with acute respirat**O**ry distress sy**N**drome

～The ICU LIBERATION Study～

Study Protocol

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• **0. Study Summary**

Study Title	ReLatIonship BEtween implementation of evidence-based and suppoRtive ICU cAre and ouTcomes of patIents with acute respiratOry distress syNdrome ～The ICU LIBERATION Study～
Background	Acute respiratory distress syndrome (ARDS) is a condition associated with hypoxemia due to noncardiogenic causes and results in high mortality. However, the epidemiology and treatment strategy for ARDS may have changed significantly due to the accumulation of a large body of knowledge, following the two-year pandemic of the novel coronavirus (SARS-CoV-2) of which the primary manifestation is ARDS. To improve the quality of ICU care that patients receive after admission to the ICU, a variety of academic societies, including the Japanese Society of Intensive Care Medicine and the Society of Critical Care Medicine, are currently developing evidence-based guidelines and consensus guidelines and statements regarding ABCDEF bundles, nutritional therapy, ICU diary. The ABCDEF bundle, nutritional therapy, and ICU diary have been developed and are being promoted for implementation in hospitals around the world. The implementation of evidence-based ICU care is strongly recommended, especially for patients with acute respiratory distress syndrome who frequently require ventilators to maintain their lives, because their patient outcomes are worse than those who were admitted to ICU with other causes. However, there is still little evidence on how the quality of ICU care (compliance rate) correlates with patient prognosis and outcomes, and there are currently no clear goals or indicators for the ICU care we should develop.
Aim	This study aims to investigate the epidemiology and treatments given to the patients and evaluate the implementation of evidence-based ICU care and its association with the outcomes of patients with acute respiratory distress syndrome admitted to the ICU. The contents of mechanical ventilation settings, respiratory conditions, and the evidence-based ICU care, such as analgesia, sedation, rehabilitation, and nutrition, given to the patients will be collected in a daily basis. Aim 1: Epidemiology Aim 2: Treatments Aim 3: Evidence-based ICU care
Study Design	International Multicenter Prospective Observational Study
Participants	Inclusion criteria (1) Patients on an invasive or non-invasive ventilator within 24 hours of ICU admission (2) Patients expected to be on an invasive and/or non-invasive ventilator for more than 48 hours (3) Patients who meet the diagnosis of ARDS within 24 hours of ICU admission Exclusion criteria

	(1) Patients who are younger than 16 years old (2) Patients with terminal conditions at the time of ICU admission (3) Patients who have been admitted to the ICU with a terminal care policy or who are expected to be admitted to the ICU with a terminal care policy within 24 hours of admission to the ICU (4) Patients who have expressed their refusal to have their clinical data used in research.
Target number of cases	Based on the sample size calculation, the target sample size is 1000 cases, with 100 sites expected to participate. Each site will be expected to enroll 10 consecutive patients, up to 20 patients.
Study Period	Research period: January 1, 2022 (or the date of ethical approval) - December 31, 2031 Total study period: 10 years Patient enrollment period: Jun 1, 2023, to May 31, 2024: 12 months
Data Collection Method	All data will be collected on a central database, the Online EDC. Online EDC is managed in the cloud and is managed under standard security measures.
Research Organization	**The central organization** LIBERATION Study Steering Committee The Japanese Society for Early Mobilization Principal investigators: Dr. Keibun Liu/ Kensuke Nakamura **Core-Research members (LIBERATION Study Steering Committee members)** (Japan) • Kensuke Nakamura, Doctor, Department of Emergency Medicine, Teikyo University Hospital • Keibun Liu, Intensive Care Collaboration Network • Hajime Katsukawa, Physical Therapist, Japanese Society for Early mobilization • Tadahiro Goto, Chief Scientific Officer, TXP Medical Corporation; Visiting Scholar Researcher, Department of Clinical Epidemiology and Health Economics, School of Public Health, The University of Tokyo • Yohei Okada, Doctor, Department of Preventive Services, Graduate School of Medicine, Kyoto University • Shunsuke Taito, Physical Therapist, Department of Clinical Practice and Support, Hiroshima University Hospital • Hideaki Sakuramoto, Nurse, Department of Critical care and Disaster Nursing, Japanese Red Cross Kyushu International College of Nursing （International） • Stefan J Schaller, Deputy Clinical Director, Department of Anesthesiology and Operative Intensive Care Medicine (CVK, CCM), Charité – Universitätsmedizin Berlin, Germany • Bernat Planas-Pascual, PT, Physiotherapy and Occupational Therapy

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1. Background and significance of the study

1.1. Background

Acute respiratory distress syndrome (ARDS) is a condition associated with hypoxemia due to noncardiogenic ccauses with bilateral lung infiltrates on chest X-ray or CT imaging (1). The 10% of all ICU admissions are ARDS patients, and the recent pandemic of the novel coronavirus has dramatically increased the number of ARDS patients in ICUs across the world. The international epidemiological study (2016) reported a mortality rate of 35-46% for ARDS, and this is very high mortality compared to other ICU diseases (2). Furthermore, ARDS survivors present with many functional impairments, including physical, cognitive, and psychiatric dysfunction (Post Intensive Care Syndrome, PICS), and their Activities of Daily Living (ADL) and Quality of Life (QOL) are impaired and many other functional impairments have been pointed out. Their inability to get their original life has attracted significant research attention and become a significantly important research topic (3). Many patients who are unable to return to work due to functional disability require nursing care, and there is concern about the increased burden on the patient, the family supporting the patient, and the social economy (4). Therefore, the development of effective strategies for patients with ARDS that take into account not only mortality, but also functional prognosis is sstrongly needed. (5).

Recent studies have shown that lung-protective ventilation (low tidal volume and airway pressure control), neuromusclular blocking agents, prone position, noninvasive mechanical ventilators, and extracorporeal membrane oxygenation (ECMO) have improved outcomes, including mortality, in patients with ARDS (2, 6-10). However, the mortality of patients with ARDS is still as high as 40%. In addition, the complete reintegration ratio of patients with ARDS after 1 year of hospital discharge reported in 2003 was only 50%, and recent reports have shown little progress in this aspect (11). Strategies to improve outcomes (mortality and functional prognosis) of ARDS patients by improving not only treatment but also the quality of ICU care have become a hot topic in recent years (12). The previous paper showed that excessive sedation and absolute bed rest for the purpose of ventilation control and rest during intubation in ARDS patients correlated with delirium, prolonged duration of ventilation, and even increased mortality (13). Therefore, attempts have been explored to improve outcomes for ARDS patients by systematically providing sedation, analgesia, rehabilitation, spontaneous breathing and awaking tests, and delirium management during ICU admission. These attempts, known as the ABCDEF bundle, have been actively recommended by number of academic societies to be introduced in ICUs as an attempt to improve outcome of patients with ARDS and promote their reintegration into society (12, 14). (ABCDEF bundle: A (Assess, prevent, and manage pain), B (Both spontaneous awakening trials (SAT) and spontaneous breathing trials (SBT)), C (Choice of analgesia and sedation), D (Delirium: assess, prevent, and manage), E (Early mobility and exercise), F (Family engagement and empowerment)), and even ICU care such as nutritional therapy and ICU diaries have been shown to improve outcomes for ICU patients, including ARDS, and are strongly recommended (12, 15). (In this study, these ICU care are referred as evidence-based ICU care.)

On the other hand, our research team has reported that the overall implementation rate of these evidence-based ICU care, ABCDEF bundles, nutritional therapy, and ICU diaries in ICU patients is quite low, and the rate is significantly lower in mechanically ventilated patients (16, 17). The reasons for the low implementation rates are thought to be that the ventilator is a major barrier. Although many articles have proposed evidence-based ICU care, there is little evidence as to which of these should be prioritized and which should be combined to maximize patient outcomes. The reason for this may be that there is a lack of evidence on which of these should be prioritized and which should be combined to maximize patient outcomes. Implementation of evidence-based ICU care requires many resources and effort, and it is difficult to implement all of them simultaneously. Therefore, the purpose of this international multicenter study is to investigate the current epidemiology and treatment strategy given to the patients with ARDS after the two-year pandemic of the novel coronavirus, clarify the actual implementation of ICU care for ARDS patients who require ventilators at high frequency, and evaluate how the implementation of evidence-based ICU care is associated with patient outcomes.

1.2. Significance of the study

This study has the potential to increase the generalizability of the results which will be obtained from all regions of the world, including Asia, Europe, North and South America, Oceania, and Africa. Therefore, the results will potentially contribute to improving patient treatment and outcomes in all regions of the world. Furthermore, the results obtained will provide a detailed picture of the current ICU care given to patients with ARDS in the ICU. The association/correlation analysis between its implementation and patient outcomes will identify the content of ICU care which can maximize improvement in outcomes for ARDS patients. As a result, this study will contribute to the development of ICU care guidelines and thereby improve the outcomes of patients with ARDS. The study will play a significant role in improving outcomes for patients with ARDS worldwide. In addition, the results of this study will serve as basement data for future interventional research.

1.3. Study Design

Due to the nature of this prospective observational study, it is not possible to prove a causal relationship between ICU care and patient outcomes. However, a randomized controlled trial of evidence-based ICU care as an intervention is considered a very high hurdle to conduct due to ethical aspects for the group that does not receive the intervention. Therefore, we are unable to conduct a randomized controlled trial at this time and have decided that an observational study is the best research design. However, this study will extract factors that are strongly associated with patient outcomes by collecting details of daily ICU care and treatment, which have not been available in previous studies, and will consider setting up interventions and randomized controlled trials based on our results.

2. Aim of the study and evaluation items

2.1. Study Hypothesis

(ⅰ) Mortality in ARDS patients has improved compared to previous reports.
(ⅱ) The treatment offered to patients with ARDS has changed compared with previous reports.
(ⅲ) If the quality of ICU care (implementation ratio) for patients with acute respiratory distress syndrome receiving non-invasive/invasive mechanical ventilation is higher, patient outcomes will be better.

2.2. Aim of the study

(ⅰ) To investigate the epidemiology of patients with ARDS on non-invasive/invasive mechanical ventilation admitted to the ICU (including short-term post-hospital discharge employment status, quality of life, physical, cognitive and mental dysfunction)
(ⅱ) To investigate the treatment provided to patients with ARDS on non-invasive/invasive mechanical ventilation admitted to the ICU.
(ⅲ) To investigate the implementation of evidence-based ICU care and its association with patient outcomes.

This study aims to establish an international registry in collaboration with institutions around the world.

2.3. Evaluation items (summary)

The following items will be collected in this study
(ⅰ) Epidemiology: mortality (survival rate), length of ICU/hospital stay, mechanical ventilation period,

etc.

(ⅱ) Treatment: the achievement of lung-protective ventilation, mechanical ventilation setting, prone positioning, neuromuscular blockade, dialysis, etc.

(ⅲ) Evidence-based ICU care

1) ABCDEF bundle implementation ratio (Attachment file 1)
2) Evaluation of PADIS and its compliance status (Attachment file 2)
3) Nutrition
4) ICU diary
5) The presence or absence of physical restraints
6) Sleep, etc.

*Data on ventilator settings, respiratory status and evidence-based ICU care will be collected daily from ICU admission until ICU day 14 or the ICU discharge day, whichever is earliest.

3. Study Design

3.1 Study Design

International Multicenter Prospective Observational Study

3.2. Study Period

Study period: January 1, 2022 (or the date of ethical approval) - December 31, 2031
Total study period: 10 years
Patient enrollment period: June 1, 2023, to May 31, 2024
Total enrollment period: 12 months
(Each institution has a limitation on the number of patients to enroll, see 3.4. Study participants below)

3.3. Participating sites

This study will be conducted under the support of the Japanese Society of Early Mobilization, in collaboration with a number of academic societies in each country and research institutions recruited through regional coordinators.

All ICUs, including adults and mixed ICUs but not pediatrics, can participate in this study. If a hospital has more than one physically and functionally different ICU, they can be registered as a separate collaborating institution. The list of participating sites and the list of principal investigators of each collaborating institution will be managed by the Research Office.

3.4. Study Participants (patient enrollment criteria)

Inclusion criteria

1) Patients on an invasive or non-invasive ventilator within 24 hours of ICU admission
2) Patients who are expected to be on an invasive and/or non-invasive ventilator for more than 48 hours in total
3) Patients who meet the diagnosis of ARDS within 24 hours of ICU admission

*The following Berlin definition of ARDS will be used

1) Acute onset (within 1 week of an apparent trigger or the appearance or worsening of respiratory symptoms)
2) Chest imaging (plain X-ray/CT) (pleural effusion, atelectasis, bilateral shadows that cannot be explained by nodules alone)
3) Causes of pulmonary edema (cannot be explained by cardiac insufficiency or excessive fluid infusion alone)
4) Impaired oxygenation (PEEP/CPAP ≥ 5 cmH2O and P/F ratio < 300 mmHg)

The severity of ARDS is classified according to the P/F ratio, and a computer algorithm is used to classify the severity of the disease based on a data set extracted from daily data.

Exclusion criteria

1) Patients who are younger than 16 years old
2) Patients with terminal conditions at the time of ICU admission
3) Patients who have been admitted to the ICU with a terminal care policy or who are expected to be admitted to the ICU with a terminal care policy within 24 hours of admission to the ICU
4) Patients who have expressed their refusal to have their clinical data used in research.

In principle, each center should aim to register 10 cases (a total of 10 cases for both survivors and deaths). The maximum number of patients to be enrolled at each collaborating intensive care unit is 20.

3.5. Duplicate Enrollment with Other Studies

Since this is an observational study, simultaneous participation and institutional enrollment in other observation and intervention studies are acceptable.

3.6. Evidence for scientific rationality

Regarding the items to collect in this study, documents such as Case Report Forms or specific Electrical Data Capture (EDC) with instructions will be prepared as appropriate so that the evaluation methods can be standardized at each facility. In addition, structural factors of hospitals and ICUs, such as each protocol for ICU patients and staff work schedules, will be investigated in advance at the time of participation of each facility and will be considered for use as adjustment factors when analyzing the results.

4. Research Methods and Procedures

4.1 Outline of Research Methods

This study will be a prospective observational study, with case enrollment beginning after Ethics Committee approval during the patient enrollment period. Up to 10 patients who meet the inclusion and exclusion criteria will be enrolled in the central online database. Upon admission to the ICU of patients who meet the selection criteria, the principal investigator or collaborator at each collaborating institution will assess their suitability for the study (e.g., checking exclusion criteria) and enroll those patients who are eligible for the study. At that time, another collaborator should conduct a confirmatory screening to ensure that the eligibility of the patient is correct. The investigator who conducts the screening should be a research collaborator consisting of several persons selected at each site, including the principal investigator, regardless of job title.
For those from the countries with regulated by General Data Protection Regulation (GDPR) (i.e., European countries), data to be collected in the study will be documented on paper CRF using an identification code (pseudonym) of the patient. After the CRF is finalized for a. patient and signed by the local investigator, anonymization will occur: The identification code will be erased so that there is no backtracking to the patient possible. After the anonymization process, the data of a patient can be entered into the electronic database (eCRF).
For those from the countries outside ot the regulations, data to be collected in the study will be entered directly into a dedicated online database. At that time, a specific identification code (patient registration number) will be created using a method that does not have the medical record ID, and an anonymization correspondence list will be created separately from the database.
No personally identifiable information or pseudonym will be entered into the database.

※How to create a patient registration number
Facility number (2 digits) - Patient number (2 digits)
For example, for the 9th registered patient at ○○ Hospital (facility number: 1), the patient registration number would be 01-09

4.2. Content of collected Information

Only clinical routine data will be collected. If centers wish to add additional analyses (e.g. blood gas tests, blood analysis and urines), this has to be discussed with their IRB.
The items to be obtained are listed below.

4.2.1 Patient characteristics (obtained upon ICU admission)

- Age, sex/gender, height, weight, BMI (automatic calculation), the month of hospital admission, the month of ICU admission
- Clinical Frailty Scale (Pre-hospital admission)
- Chronic diseases (chronic lung disease (including COPD, interstitial pneumonia, etc.), chronic renal failure, dialysis, heart failure NYHA III-IV, home oxygen/ventilator, active malignancy, hematologic disease)／Charlson Comorbidity Index
- Presence of ARDS risk factors (Direct factors: pneumonia and other respiratory infections, aspiration of stomach contents, Inhalation Injury, pulmonary contusion, pulmonary vasculitis, thoracic trauma, drowning, In-Direct factors: non-pneumonia sepsis, non-thoracic trauma, pancreatitis, burn, non-cardiogenic shock, drugs Overdose, transfusion-related lung injury, and Other: influenza, novel coronavirus, other text input), and possible cardiogenic hypoxemia.
- Pre-admission Barthel Index (family estimates are acceptable), pre-admission dementia (Clinical Dementia Rating, CDR: mild, moderate, severe), pre-admission psychiatric illness (depression, schizophrenia, etc.), pre-admission employment status、Pre-admission Functional Oral Intake Scale (FOIS)
- Severity score at the time of ICU admission: Sequential organ failure assessment (SOFA score), APACHE II (on admission to ICU)
- Other items may be added as necessary.

4.2.2 Evidence-based ICU care and treatment which will be collected in a daily basis from the first day of ICU admission to ICU 14 days or the date of ICU discharge, whichever is earliest.

- Multidisciplinary rounds (If yes, the type of professions leading the round and the presence of family members or key persons involved in the round)
- ABCDEF bundle

  A (Assess, prevent, and manage pain) = the presence of pre-determined goal, the achievement of the pre-determined goal, contents and number of times pain assessment tools were used,

  B (Both spontaneous awakening trials (SAT) and spontaneous breathing trials (SBT)) = Whether SAT was performed during non-invasive ventilation or SAT and SBT during invasive ventilation. If not done, also select the reason for the survey in a pull-down format.

  C (Choice of analgesia and sedation) = Data regarding Analgesia will be described in A. The focus here is primarily on sedatives.
  the presence of pre-determined goal, the achievement of the pre-determined goal, the sedation assessment tool and the number of times it has been used, and the use of pharmacologic interventions (if yes, → describe the detail).

  D (Delirium: assess, prevent, and manage) = content and number of assessments of delirium assessment tools, presence or absence of delirium (if yes → number of times it became positive),

  E (Early mobility and exercise) = Rehabilitation content based on the ICU Mobility Scale (IMS) and duration of rehabilitation performed, (If two or more rehabilitation sessions were performed, list more than one) the presence of pre-determined goal (if yes → indicated by IMS)

  F (Family engagement and empowerment) = whether the patient and family met (if yes → in-person or virtual, and time of meeting)
- Nutritional therapy = route of nutritional administration (intravenous, enteral with/without oral), estimated calories and protein given (for each route separately), presence of adverse events (if yes, select main adverse events in pull-down form),
- Use of ICU diary, and who should fill it in (family, staff, or other).

- Arterial blood gas (enter the arterial blood gas results when PaO2 was the worst of the day): pH, PaO2, PaCO2, Lactate, P/F ratio (automatic calculation) .

- Ventilator-related factors: ventilator settings when the above blood gas results were obtained (respiratory mode, FIO2, set respiratory rate, actual respiratory rate, actual minute ventilation rate, PEEP, Plateau pressure (if available), driving pressure (automatic calculation), the presence of spontaneous breathing P0.1, and Peak inspiratory pressure, and other factors).

- Severity score: SOFA score.

4.2.3. Data related to treatment during ICU stay (not daily basis)

- Steroid (if yes, start date, number of days of the administration, and total daily dose), continuous neuromuscular blockade (if yes, type of drug, start and end date), prone position (if yes, start and end date of administration and average time per session), and dialysis (if yes, start date and type of continuous hemodiafiltration (CHDF), intermittent hemodiafiltration (IHDF)), cytokine adsorption therapy (if yes, start date and type; polymyxin B-immobilized fiber column; PMX/AN69ST/ CytoSorb), use of the following modes of extracorporeal membrane oxygenation (VV-ECMO, VA-ECMO, VVA-ECMO, VAV-ECMO), Tracheostomy Surgery (if yes → date and content) Swan-Ganz (if yes → start date), esophageal maneuver (if yes → start date), EIT (if yes → start date), echocardiography (if yes → start date), pulmonary echo (if yes → start date), recruitment maneuvers (if yes → start date, the maximum pressure during the procedure, and its time)

- ICU care-related data: ABCDEF bundle (A: the use of the pharmacological intervention (select from a list → the first day of ICU admission to use it), the use of the non-pharmacological intervention (select from a list → the first day of ICU admission to use it), D: presence of pharmacological intervention (select from a list → the first day of ICU admission to use it) presence of non-drug intervention (select from a list → the first day of ICU admission to use it), F: Whether information on PICS was provided to family members, whether family members participated in ICU care such as ABCDE on that day (select from a list → the first day of ICU admission to use it, and frequency),), Physical restraints (if any→duration of use), intervention of speech therapist (if yes → the contents of assessment: RSST:Repetitive　Saliva Swallowing Test or MWST：Modified Water Swallowing Test, and intervention: direct or indirect swallowing rehabilitation)

- Routine blood tests at the day of 14 days (± 2 days) after ICU admission regardless of the location where the patients are when blood is taken, even in general ward: White Blood Cell count, neutrophils count, lymphocyte count, Alb, and CRP levels.
  If patients discharge until 14 days after ICU admission, the data will not be collected.
  If routine blood tests are not done at a center, the center may discuss additional blood tests for research purpose with their IRB.

- Routine clinical imaging at following specific times will be marked/clicked on the EDC only if taken (not upload at this stage):
  X-ray: ICU admission, non-invasive/invasive mechanical ventilation initiation, ECMO initiation, weaning from ECMO, weaning from non-invasive/invasive mechanical ventilation, ICU discharge, and hospital discharge
  CT images: ICU admission, non-invasive/invasive mechanical ventilation initiation, ECMO Initiation, weaning from ECMO, weaning from non-invasive/invasive mechanical ventilation, ICU discharge, and hospital discharge

4.2.4. Patient outcomes

- Day since ICU admission when noninvasive ventilator start/end, invasive ventilator start/end, ECMO start/end, ICU discharge, hospital discharge, and/or death date
- Length of ICU and hospital stay (automatic calculation) , total duration on non-invasive/mechanical ventilation and/or ECMO (automatic calculation)

- Complications during ICU stay (e.g., ventilator associated pneumonia, pneumothorax, etc.) if yes → Day since ICU admission
- Clinical Frailty Score,
- Physical function assessment at ICU discharge (Medical research council sum-score)
- Swallowing function (routine clinical data only): Functional Oral Intake Scale (FOIS) at ICU and hospital discharge and specific timings
- Destination after hospital discharge (direct to home, general hospital, rehabilitation hospital, nursing home, etc.) If discharged home, do they live alone or with family members?
- Respiratory support at discharge (oxygen, noninvasive ventilatory management, invasive ventilatory management)
- Tracheostomy during hospitalization
- Causes of death (multiorgan failure, respiratory failure, heart failure, liver failure, cardiovascular events, septic shock, hemorrhagic shock, other, not applicable)
- Physical function at discharge: Barthel Index, grip strength
- Quality of life at discharge: EQ-5D-5L, EQ-VAS
- Cognitive dysfunction at discharge: Mini-Mental State Examination (MMSE)
- Mental function at discharge: Hospital Anxiety and Depression Scale (HADS), Impact of Events Scale-Revised (IES-R).

- Other items will be added as needed.

4.2.5. Telephone follow-up (only once 3 months after discharge)

Survival or not (date if death), readmission to ICU/hospital or not, employment status, Clinical Frailty Score, Barthel Index, EQ-5D-5L, EQ-VAS, MMSE (telephone version), HADS, IESR.

The explanation is given to the patient or family members (key-person) using an explanatory document at the time of ICU admission, and telephone follow-up is conducted only when the patient or family members (key-person) provide the consent. If the patient has died, the date is confirmed with the family and further follow-up is terminated.

4.2.6. <u>Optional</u> (only for the participating sites in Japan that agree to collect these items)

- Blood tests: Two blood tests should be performed on days 3 (2-4) and 14 (12-16) after ICU admission. The blood sample is collected in an EDTA-containing blood sample tube, centrifuged at 3000 rpm for 15 minutes (4°C), and then the supernatant fluid is collected and stored at -80°C. The blood sample is also transported at -80°C.

- Urinalysis: A spot urinalysis will be performed on day 3 (or 2-4) of ICU admission to obtain urinary creatinine and urea nitrogen levels, and the urine sample obtained at the same time will be stored frozen (-20°C).

4.2.7. Basic Institutional background Information (These items are registered as basic background information prior to the start of the study.)

Number of hospital beds, hospital type, number of ICU beds, patient-nurse ratio, patient-physician ratio, ICU type, availability of dedicated intensivists, physical therapists, occupational therapists, speech therapists, respiratory therapists, availability of various protocols for ICU care, pre-set visiting hours, availability of brochures on PICS, etc.

4.3 Creation and management of EDC and central data server

All data will be collected on the online database (EDC) with standard security, which is cre ated exclusively for this research registry. The information in the database is already anony mized, with no names, addresses, images of the patient face, or other information that can identify the patient (like dates or pseudonym). Patient will be informed that at the end of th eir data collection at 3 months, their data will be anonymized to include in the online datab ase. When information in this database is to be extracted, it will first be extracted by the

Research Office via the Internet in a password-protected state and stored at the Research Office. The extracted master data is stored at the Research Office, and a password-protected copy is submitted to the person in charge of analysis. In this case, the Research Office will keep a complete history of the data, including when and to whom it was submitted, and its purpose.

In the database collected in the central database, cases registered from each participating site will be seen only by the facility concerned. In other words, Hospital A can only view the data of cases registered from Hospital A, and cannot view or manipulate any data from other hospitals.

4.4 Outcomes

(ⅰ) To investigate the epidemiology of patients with ARDS on non-invasive/invasive mechanical ventilation admitted to the ICU (including short-term post-hospital discharge employment status, quality of life, physical, cognitive and mental dysfunction)

Primary endpoint: mortality (in-hospital mortality, mortality at 3-month after discharge)

Secondary endpoints: length of ICU/hospital stay, duration on ventilator, ventilator withdrawal rate, etc.

(ⅱ) To investigate the treatment provided to patients with ARDS on non-invasive/invasive mechanical ventilation admitted to the ICU.

Primary endpoint: The achievement of lung protective ventilation (TV < 6-8 ml/kg, plateau pressure < 25-30 cmH2O, driving pressure < 15 cmH2O).

Secondary endpoints: data on how to use non-invasive/invasive ventilation, prone positioning, neuromuscular blockade, dialysis, etc.

(ⅲ) To investigate the implementation of evidence-based ICU care and its association with patient outcomes

After dividing patients into two groups (<30% and ≥30% implementation rate), the following endpoints will be evaluated.

Primary endpoint: Mortality at hospital discharge and 3-month thereafter

Secondary endpoints: duration of mechanical ventilation, duration of ECMO use, ICU length of stay, hospital length of stay, duration of delirium, physical, cognitive and mental function, quality of life, etc.

Follow the investigation of the implementation of ICU care such as ABCDEF bundle, nutritional therapy, ICU diary, physical restraints, etc., and the association between the above patient outcomes and outcomes will be investigated.

※As this study aims to establish a registry with the potential to enroll a large number of patients, additional analyses will be performed as needed.

4.5 Sample size

For research aims (ⅰ) and (ⅱ), no clear sample size is set, as these are observational studies aiming to collect epidemiological data as the main objective. For research aim 3, assuming an α error of 0.05 and a 1-β error of 0.90 for the two groups (implementation ratio <30% and ≥30%), and estimating the mortality for each group as follows, the required sample size is as follows.

Mortality; 10% vs. 20% 286 participants in each group, total 572 participants
Mortality; 15% vs. 25% 355 participants in each group, total 710 participants
Mortality; 20% vs. 30% 412 participants in each group, total 824 participants
Mortality; 25% vs. 35% 460 participants in each group, total 920 participants
Mortality; 30% vs. 40% 376 participants in each group, total 752 participants
Mortality; 35% vs. 45% 396 participants in each group, total 792 participants

From the above, a total of 1000 cases, 500 cases each, could be collected for analysis on sufficient sample size. Based on our previous studies, we expect 100-200 ICUs to participate, to enroll 10

cases per ICU.

5. Informed Consent

This study, as a prospective observational study, requires, in addition to the usual medical care, functional assessment at discharge, and follow-up on quality of life after discharge. Optional is the additional acquisition of blood and urine test data, storage of blood and urine samples only for the participating sites in Japan where agreed to send these samples with appropriate approval by their local IRB..

Patients will be only included after written informed consent by the patient or a legal proxy. It is to be expected that patients in this study will not be capable of consenting at study inclusion, i.e. a proxy according to local regulations will be asked. If inclusion occurred by proxy, patient consent should be obtained within the hospital stay, if the patient's condition allows it. If this is not possible, oral consent at the telephone interview at 3-months follow up from the patient will be attempted a last time. (Note: If the patient is also unable to consent at this time, the consent of the legal representative remains the appropriately valid one).

Local regulations of each center have precedence above the here described pathway.

※Explanation of the possibility of a very small invasive procedure

In this study, there are laboratory blood test and urine test. The laboratory tests are the standard and routine laboratory tests for patients with ARDS. Centers can opt in for blood tests and urine analysis at specific time points (see above), however, this is optional only. Blood and urine samples are collected using the usual blood and urine collection methods, and the level of invasiveness is the same as that of usual medical examinations. This should be included in the patient informed consent form and the consent of the patient or relatives should be obtained.

To ensure transparency, this study will be registered with UMIN or Clinical Trial Gov.

6. Statistics

Nominal variables are presented as numbers and percentages and are analyzed using the chi-square test or Fisher's exact test appropriately. Continuous variables are presented as mean and standard deviation for parametric distributions and median and interquartile range for non-parametric distributions. Comparisons of continuous variables are performed using one-way analysis of variance or Mann-Whitney U-test appropriately. To examine the association between implementation of evidence-based ICU care and patient outcomes, the statistical analysis methods will be selected with help of statisticians. Multivariate analyses such as multivariate logistic regression analysis or multivariate linear regression analysis will be used to evaluate independent factors with specific outcomes. All statistical tests were two-sided and used 5% as a significant difference.

7. Sample and Data Management

The collected data handled in this study will be stored in an online database system (EDC), and as described in 4.3, the cases registered from each participating site can only be accessed by the relevant participating site on the database collected in the central database. In other words, the hospital A can only view and edit the data of cases registered from the hospital A and other hospitals/ICUs cannot view or manipulate the data from the hospital A.

These study data will be extracted using the process specified in 4.3, and the data will be directly extracted to the study office without any information that identifies the individuals. The chief investigator of each participating site will store all documents or records related to this study to ensure the reliability of the data until five years (or according to local regulations) have passed since the study is completed. After that, the research materials will be deleted with maximum caution for personal information. (Note: Anonymous data do not have to be destroyed as they no longer

constitute personal data.)

Regarding the images (X-ray and CT scanning images), when data extraction is performed at each facility, the data should be extracted with information that may identify individuals, such as name, hospital ID, and the date and time of imaging, remove. Only when these extracting measures can be applied, the data should be sent to the Data Management Office in a standard password-secured state.

※Blood and urine samples that may be obtained as an option only for the participating sites in Japan where agreed to send these samples.

- Blood tests (optional): Two blood tests will be performed on days 3 (2-4) and 14 (12-16) after ICU admission. Blood samples are collected in EDTA-containing blood sample tubes, centrifuged at 3000 rpm for 15 minutes (4°C), and the supernatant fluid is collected and stored at -80°C. The blood samples will be kept at -80°C during transport.

- Urine Samples (optional): Urine samples should be frozen at -20℃ or cooler after collection. After six months to one year of storage, the specimens will be delivered by frozen courier service. Since this urine specimen does not contain any specific pathogens and does not fall under category A/B based on the WHO Guidance on the Regulation of the Transport of Infectious Materials, it can be judged as a non-eligible product (e.g., a sample that is extremely unlikely to contain live pathogens) and can be transported using the normal frozen courier service. As for the packaging, since it is a non-pathogenic product with extremely low pathogenicity, the requirements for hazardous material transport are not considered applicable based on the WHO Guidance on the Regulations for the Transport of Infectious Materials, and no special labeling or container is required. The cost of transporting the stored urine samples will be covered from the research funds obtained for this study.

※Transportations from overseas collaborative study Implementing facility

Samples will be collected and stored at overseas participating sites, where agree to collect these samples with the informed consent from the patient, in the same manner as described above. Since the specimens can be analyzed after several years of storage, they will be transported sequentially as soon as funding is available. The LIBERATION Study Research Office will cover the transportation costs.

8. Study management

8.1. Study progress control

Monitoring of the progress of this study will be conducted by The LIBERATION Study Research Office.

8.2. Monitoring

Monitoring of the collected data will be performed by the LIBERATION Study Research Office. The LIBERATION Study Research Office may inquire about the input of data to facilities where data input is lacking or where input data is found to be incomplete. However, especially for those from the countries with regulated by GDPR (i.e., European countries), since the data is anonymized, the local investigators have to ensure adequate data quality and completeness because after anonymization there is no possibility to view the patient data again for a quality check. Therefore the paper CRF should clearly state if values were not able to be obtained and the local investigator has to sign off the CRF before anonymization occurs.

8.3. Auditing

Audits will not be conducted.

9. Ethics and Guideline Principles

9.1. Complying with Guideline Principles

Declaration of Helsinki (revised October 2013), Ethical Guidelines for Medical and Biological

Research Involving Human Subjects (Ministry of Education, Culture, Sports, Science and Technology, Ministry of Health, Labour and Welfare, Ministry of Economy, Trade, and Industry, March 23, 2021), and the Act on the Protection of Personal Information (Revised April 2022). For Europe, General Data Protection Regulation (GDPR) applies until the anonymization process.

9.2. Preparation and Revision of Documents and Consent Forms

The chief investigator at each participating site should be responsible for preparing the Information document, and consent and consent withdrawal form based on the documents provided by the LIBERATION Study Research Office, and revisions of each document should be approved by the local ethics committee at each participating site.

9.3. Obtaining Permission at each participating site

Since this study will be conducted as a multi-center study, the chief investigator at each participating site shall obtain the ethical approval by the local Ethics Committee to conduct this study according to local regulations. Since the overseas laws and regulations related to clinical research may differ, it is assumed that approval by the ethic committee will be necessary as appropriate at each participating site.

9.4. Protection of Personal Information

All investigators should comply with the "Declaration of Helsinki (revised October 2013)" and the " Ethical Guidelines for Medical and Biological Research Involving Human Subjects (March 23, 2021, Ministry of Education, Culture, Sports, Science and Technology, Ministry of Health, Labor and Welfare, Ministry of Economy, Trade and Industry)" and relevant laws, guidelines, and ordinances regarding the handling of personal information.

Especially for those from the countries with regulated by GDPR (i.e., European countries), each center will have a patient identification list which names the names and the pseudonym of the patient. However, if a paper CRF of a patient is finalized and signed of as valid by the local investigator, the pseudonym of the patient will be erased (cut off) the paper CRF, i.e. there is no tracing back to the patient possible (anonymization). After that the anonymized patient data can be put into the database. No other center or the research office will be granted access to the patient identification list, which is stored by each local chief investigator.

The database does only collect anonymized information as described by the process above. Therefore, no personal information such as name, date of birth, or patient ID or dates (if regulated by the local law) will be included in the database.

Data extracted from the central database managed by the LIBERATION Study Research Office will be stored in password-protected files and USB memory devices in the safekeeping of the Research Office.

In principle, all persons involved in this study are obligated to maintain confidentiality and to make every effort to protect personal information. This study will be conducted in compliance with the "Guidelines for the Appropriate Handling of Personal Information by Medical and Nursing Care Professionals" and will be conducted with the greatest caution in handling patients' personal information. The scope of those who handle personal information and personal data is limited to the chief investigator at each participating site, research collaborators and research assistants within the same participating site. In the event of leakage or loss of personal information, local regulation have to be followed.

※Each country may have different legal and regulatory requirements that must be complied with, so consider incorporating legal and regulatory requirements into the study protocol as appropriate to the circumstances in each country.

9.5.1. Burden and potential adverse effects of participation in the study

This survey will be performed without any burden to patients and their families since evidence-based ICU care provided within the scope of usual medical care is extracted from the medical records of each participating site.

9.5.2. Predicted Benefits of participation in the study

Participation in this study will provide insight into the actual ICU care that patients with ARDS in ICUs receive. Clarifying the actual treatment and ICU care being provided and identifying the independent factors that contributes to ARDS patient outcomes may lead to the creation of appropriate guidelines or ICU bundled care in the ICUs across the world.

10. Funding

10.1. Sources of study Funding and Conflicts of Interest

This study was funded by the Japanese Association of Acute Medicine (JAAM) as an association-leading multicenter study, and by Dräger Japan Co. Ltd. However, neither the Japanese Association of Acute Medicine nor Dräger Japan will be involved in any way in the planning, design, execution, implementation, analysis, and publication of this research project. Conflicts of interest of the researchers in this research project are properly managed by the respective institutions to which they belong.

All investigators, including principal investigators and co-investigators, should disclose conflicts of interest when required, such as in conference presentations and publications in Journals.

10.2. Financial contribution of the participating sites for this study

This study will be performed as a treatment within the usual insurance coverage and will not result in an increase in financial burden compared to daily medical care. The LIBERATION Study Research Office will pay for the transportation of blood and urine tests, which will be collected as an option.

10.3. Compensation to individuals

This study is not covered by compensation insurance because it does not provide medical care beyond the procedures and evaluations that are performed in the usual practice. If any health problems occur to study participants as a result of this study, the department will be responsible for treating them. Treatment costs of health problems will be covered by the insurance of the participants and not paid by the LIBERATION Study Research Office.

11. Incentives to the participants

There are no rewards for patients or family members for participating in this study.

12. Study Protocol Amendments

In revising the study protocol and changing the investigators, the chief investigator at each participating site shall obtain the ethical approval by the Ethic Committee about the revisions or changings.

13. Study Discontinuation

Research will be discontinued in the following cases

- If competition of this study is considered to be difficult due to frequent deviations from the study protocol or for other reasons.

14. Second Data Analysis / Sub studies

This study will build a large database, and secondary data analysis of this database may lead to the important findings to improve ICU treatment and care, thereby contributing to improved patient outcomes. Therefore, the secondary data analysis will be considered rationale or reasonable through the entire study period. The chief investigators can submit the pre-specified application form for the secondary data analysis of the database of this study to the LIBERATION Research Study Office, where will decides whether the second analysis is acceptable or not. The co-investigators and collaborators at each participating site will be also able to submit the application form with approval of the chief investigator, which will be placed on the same process of review by the Committee. The need for a review by the local ethic committee for the secondary data

analysis will be determined according to local regulations.

15. Publications and Authorship

15.1. Study registration

This study, a multicenter, prospective observational study, will be registered in the University hospital Medical Information Network - Clinical Trials Registry (UMIN-CTR https://www.umin.ac.jp/), and/or Clinical Trials. gov (https://clinicaltrials.gov/).

15.2. Publication of the results

The results of this study will be reported in a conference and in a published article.

15.3. Attribution of the results

The results of this study belong to the principal investigators, the relevant chief investigators or co-investigators/ collaborators.

16. Study Report

Reports to the director of the participating site are necessary in the following cases

- When you obtain the facts or information that fail the scientific rationale to perform this study and potentially affect the continuation of the study.
- when you obtain the facts or information that could fail the proper conduct of this study or the reliability of the research results.
- If the study is completed or discontinued.
- A annual report on the progress of the study.

17. Steering Committee

17.1. Principal Investigator

LIBERATION Study Steering Committee
Principal Investigators: Keibun Liu and Kensuke Nakamura

17.2. Research Office

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17.3. Data management office

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Eugene Wesley Ely, MD, MPH, 1. Critical Illness, Brain Dysfunction, and Survivorship (CIBS) Center, Vanderbilt University School of Medicine, Nashville, TN, USA, 2. Geriatric Research Education and Clinical Center (GRECC), Department of Veterans Affairs Medical Center, Tennessee Valley Healthcare System, Nashville, TN, USA

（References）

（1） ABCDEF bundle

A	Assess, Prevent, and Manage Pain
B	Both Spontaneous Awakening Trials (SAT) and Spontaneous Breathing Trials (SBT)
C	Choice of Analgesia and Sedation
D	Delirium: Assess, Prevent, and Manage
E	Early Mobility and Exercise
F	Family Engagement and Empowerment

(1) Pandharipande P, et al; Liberation and animation for ventilated ICU patients: the ABCDE bundle for the back-end of critical care. Crit Care. 2010;14(3):157.

（2） PADIS 2018 guideline

P	Pain (Assess, Prevent, and Manage Pain)
A	Agitation (Assess, Prevent, and Manage Agitation)
D	Delirium (Assess, Prevent, and Manage Delirium)
I	Immobility (Assess, Prevent, and Manage Immobility)
S	Sleep (Assess, Prevent, and Manage Sleep disturbance)

（3） ABCDEF バンドル

ABCDEF bundle	
A	Assess, Prevent and Manage Pain
B	Both Spontaneous Awakening Trials (SAT) and Spontaneous Breathing Trials (SBT)
C	Choice of Analgesia and Sedation
D	Delirium: Assess, Prevent and Manage
E	Early Mobility and Exercise
F	Family Engagement and Empowarment

(1) Pandharipande P, et al; Liberation and animation for ventilated ICU patients: the ABCDE bundle for the back-end of critical care. Crit Care. 2010;14(3):157.

（4） PADIS 2018

P	Pain
A	Agitation
D	Delirium
I	Immobility
S	Sleep

(2) Devlin JW、et al; Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. Crit Care Med. 2018; 46(9):e825-e873.

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