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# Effects of evidence-based ICU care on long-term outcomes of patients with sepsis or septic shock (ILOSS): protocol for a multicentre prospective observational cohort study in Japan

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## ABSTRACT

**Introduction** Sepsis is not only the leading cause of death in the intensive care unit (ICU) but also a major risk factor for physical and cognitive impairment and mental disorders, known as postintensive care syndrome (PICS), reduced health-related quality of life (HRQoL) and even mental health disorders in patient families (PICS-family; PICS-F). The ABCDEF bundle is strongly recommended to overcome them, while the association between implementing the bundle and the long-term outcomes is also unknown.

**Methods and analysis** This is a multicentre prospective observational study at 26 ICUs. All consecutive patients between 1 November 2020 and 30 April 2022, who are 18 years old or older and expected to stay in an ICU for more than 48 hours due to sepsis or septic shock, are enrolled. Follow-up to evaluate survival and PICS/ PICS-F will be performed at 3, 6 and 12 months and additionally every 6 months up to 5 years after hospital discharge. Primary outcomes include survival at 12 months, which is the primary outcome, and the incidence of PICS defined as the presence of any physical impairment, cognitive impairment or mental disorders. PICS assessment scores, HRQoL and employment status are evaluated. The association between the implementation rate for the ABCDEF bundle and for each of the individual elements and long-term outcomes will be evaluated. The PICS-F, defined as the presence of mental disorders, and HRQoL of the family is also assessed. Additional analyses with data up to 5 years follow-up are planned.

**Ethics and dissemination** This study received ethics approvals from Saiseikai Utsunomiya Hospital (2020-42) and all other participating institutions and was registered in the University Hospital Medical Information Network Clinical Trials Registry. Informed consent will be obtained from all patients. The findings will be published in peer-reviewed journals and presented at scientific conferences.

**Trial registration number** UMIN000041433.

## Strengths and limitations of this study

► This is the first multicentre prospective observational cohort study of patients with sepsis or septic shock and their families, including follow-up for up to 5 years after hospital discharge.
► An electronic data capture system was specifically created for this study, designed especially to limit missing data and lost to follow-up.
► The potential primary limitation of this study is lost to follow-up after hospital discharge, resulting in missing data which may induce bias.
► This study is performed only at participating sites in Japan and might be affected by the COVID-19 pandemic.

## INTRODUCTION

Sepsis is a worldwide threat to people because of high mortality and the development of long-lasting disabilities, including physical and cognitive impairment and mental disorders, known collectively as postintensive care syndrome (PICS), which contributes to reduced health-related quality of life (HRQoL) for several years even after successful recovery from the critically ill state.[1–5] Although the PICS can develop in all intensive care unit (ICU) populations, sepsis is regarded as a major risk factor.[6]

Sepsis survivors often need a longer period of rehabilitation, consuming more medical and social resources and struggle with financial burdens.[7–9] The development of PICS significantly correlates with increased mortality after hospital discharge.[10] ICU admission may lead to acute or sustaining psychological symptoms and reduction in HRQoL for the patient's family during and after the acute event (PICS-family; PICS-F).[11] Despite the availability of data regarding relatively short-term results, the long-term outcomes including survival and the development of PICS/PICS-F associated with sepsis are still lacking. Investigating outcomes to identify the best strategies to improve long-term prognosis and reduce the incidence of PICS/PICS-F is necessary to facilitate patient's return to their original lives.

In the current literature, evidence-based ICU care, such as the ABCDEF bundle[12] and nutrition support,[13] and other supportive ICU care including an ICU diary[14] and limiting the use of physical restraints[15] are recommended to be incorporated into routine ICU practice. The ABCDEF bundle, which includes six key evidence-based elements (A: Assess, Prevent, and Manage Pain, B: Both Spontaneous Awakening Trials and Spontaneous Breathing Trials, C: Choice of Analgesia and Sedation, D: Delirium: Assess, Prevent and Manage, E: Early Mobility and Exercise, F: Family Engagement and Empowerment), was developed to improve the quality of ICU care and has improved short-term outcomes, including hospital mortality, ICU and hospital lengths of stay, duration of mechanical ventilation, delirium and healthcare costs.[16 17] Although the potential benefits of the ABCDEF bundle on outcomes after hospital discharge have been suggested,[18] its impact on long-term outcomes is unknown. Among the six elements, determining the combination which has the greatest synergistic effect to maximise outcomes is essential to facilitate their introduction in the ICU, but there is still a lack of data to make such a determination.

We hypothesised that including evidence-based ICU care during the ICU stay is significantly associated with improved long-term outcomes. Therefore, we will conduct a multicentre prospective observational study focusing on long-term outcomes, up to 5 years after hospital discharge, including survival, development of PICS and HRQoL of patients admitted to an ICU with a diagnosis of sepsis or septic shock, and the development of PICS-F and HRQoL in their family. This study will report the implementation rate of evidence-based ICU care provided to patients during their ICU stay and its association with long-term outcomes.

## METHODS AND ANALYSIS
### Study design
The ILOSS (Investing Long-term Outcomes of Sepsis or Septic shock) study with data from follow-up assessment for up to 5 years after hospital discharge is performed as a multicentre observational prospective cohort study. This study started when the first patient was enrolled
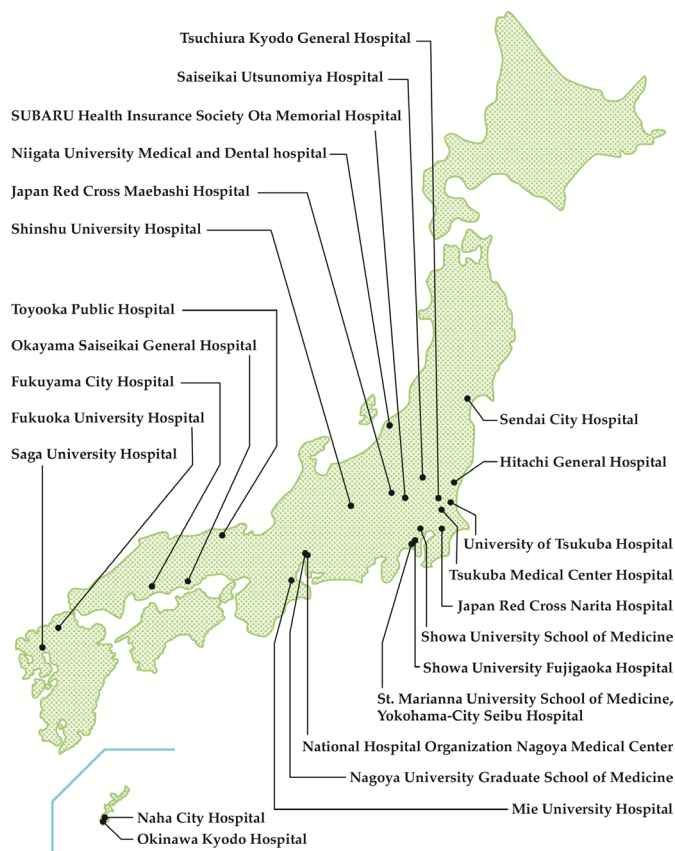


**Figure 1** Map of participating sites.

and will last until the completion of 5-year follow-up for the patient last discharged from the hospital. The study report will follow the Strengthening the Reporting of Observational Studies in Epidemiology statement: guidelines for reporting observational studies.

Twenty-six ICUs from 24 hospitals across Japan are participating in this study (figure 1). Two hospitals have two participating ICUs which differ in function and location. Of 24 participating hospitals, 14 (58%) are community hospitals and the other 10 are university or university affiliated hospitals. Most of these ICUs (85%) are mixed medical-surgical ICUs. The background information for each hospital and ICU (eg, presence of protocols specific to each element of the ABCDEF bundle, nurse to patient ratio, and availability of intensivists and other ICU professionals) is obtained before study initiation and will not change through the period of patient enrolment. All participating hospitals were not specifically trained to implement the ABCDEF bundle before the study. Although protocols for ICU care at each participating site are not unified or shared, they are developed based on the recent standard guidelines such as the 2018 Pain, Agitation/sedation, Delirium, Immobility and Sleep guideline,[19] the nutrition guidelines[13] and the guideline for mechanical ventilation management[20] depending on each ICU characteristic. All ICUs provide standardised sepsis treatment to patients according to the Surviving Sepsis Campaign 2020 by the Japanese Society of Intensive Care Medicine.[21]
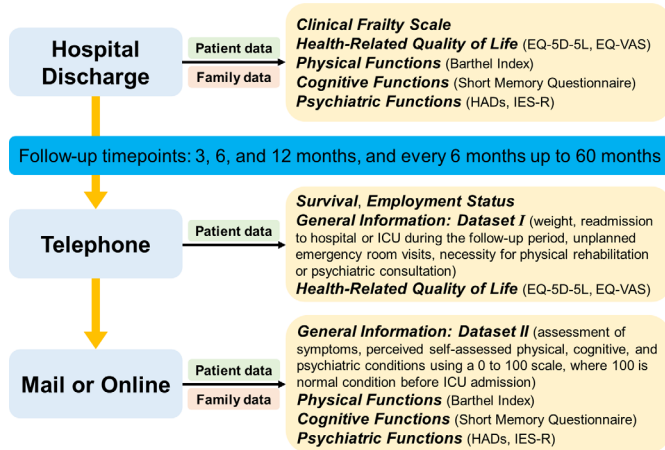
**Figure 2** Overview and outcome measures during follow-up. EQ-5D-5L, EuroQoL 5-dimension 5-level; IES-R, Impact of Events Scale-Revised; ICU. intensive care unit; EQ-VAS, EuroQoL Visual Analogue Scale; HADS, Hospital Anxiety and Depression.



**Figure 3** Availability of each assessment at follow-up. EQ-5D-5L, EuroQoL 5-dimension 5-level; EQ-VAS, EuroQoL Visual Analogue Scale; HADS, Hospital Anxiety and Depression Scale; IES-R, Impact of Events Scale-Revised.

## Patients

All consecutive patients, admitted to the ICU from the emergency room, the general ward or the operating room between 1 November 2020 and 30 April 2022, which is the patient enrolment period of this study, will be screened by participating physicians at each site. Only patients diagnosed with sepsis or septic shock according to the Sepsis-3 definition[22] at the time of ICU admission will be eligible for enrolment (online supplemental table 1). Patients who are less 18 years old or expected to be discharged from the ICU within 48 hours, cannot walk independently even with a walking aid before hospitalisation or communicate because of pre-existing psychiatric symptoms, have a central nervous system disorder that is considered not to be caused by sepsis based on clinical examination (eg, stroke, severe head trauma, brain tumour, hypoxic encephalopathy, cerebrovascular dementia and Alzheimer's disease), or are diagnosed with COVID-19 infection or are in a terminal state will be excluded since they might receive less or a different degree of ICU care than usual because of pre-existing comorbidities or specific causes of the disease.

## Follow-up

After assessment at the time of hospital discharge, a follow-up will be conducted as illustrated in figure 2. Research collaborators at each participating site will contact patients by telephone at each follow-up time-point, 3, 6 and 12 months and additionally every 6 months up to 60 months (5 years) after hospital discharge (figure 3). Survival, employment status, the general information dataset I and HRQoL (EuroQoL 5-dimension 5-level: EQ-5D-5L, and EuroQoL Visual Analogue Scale: EQ-VAS)[23] are evaluated by telephone interview (table 1). If a patient dies, the date of death will be confirmed with the family.

At the end of the telephone interview, patients are asked to choose postal mail or online for the following assessment associated PICS. Using the postal mail method, they will receive questionnaires and response sheets by postal mail for the general information dataset II, physical function using the Barthel Index (BI),[24 25] cognitive function using the Short Memory Questionnaire (SMQ),[26] psychiatric symptoms by the Hospital Anxiety and Depression Scale (HADs) for anxiety and depression,[24 27] and Impact of Events Scale-Revised (IES-R) for psychiatric assessment of post-traumatic stress disorder[24 28] (table 1). The patient can answer the questionnaires with the assistance of their family if necessary and whether they answer by themselves or with help of family is recorded. If patients develop a serious disturbance of consciousness, or severe cognitive or psychiatric dysfunction, the questionnaires for HADs and IES-R will be waived and the specific reasons recorded, while other questionnaires can be objectively answered by the family. All the completed responses will be mailed back to the central study hospital, the Saiseikai Utsunomiya Hospital and ILOSS Committee members, who are not involved in treatment or assessment of the patients, will add the results to the online database. Using the online follow-up method, the QR code linked to the online questionnaires using the same sentences and phrases as those in the postal mail method will be sent to the patients. If they answered the online questionnaire, the results will be directly reflected in the online database. Whether the patients respond via mail or online is also recorded. After making several phone-call attempts, if contact is not made with the patient or their family, patients will be regarded as lost to follow-up and excluded from analysis. Follow-up assessment for the family, including the key person for the patient's decision-making for treatment, will be performed by mail or online as the method chosen by the patient at the same follow-up timepoints.

**Table 1** Details of outcome measures at follow-up

| Variable | Description |
| --- | --- |
| Survival | If a patient dies during follow-up, date of death is recorded |
| Employment status | Whether the patient/family has a job at follow-up (full time or part time) and whether the job is the same as before ICU admission |
| General information | Dataset I: weight, readmission to hospital or ICU during follow-up, unplanned emergency room visits, necessity for physical rehabilitation or psychiatric consultation<br>Dataset II: assessment of symptoms such as shortness of breath, fatigue, appetite, perceived self-assessed physical, cognitive and psychiatric conditions scored from 0 to 100, with 100 being the condition before ICU admission |
| Health-related quality of life (HRQoL) | |
| EuroQoL 5-dimension 5-level | A 5-dimension questionnaire to measure HRQoL: mobility, self-care, usual activities, pain/ discomfort and anxiety/depression. Each dimension has five levels scored numerically: no problems=1, slight problems=2, moderate problems=3, severe problems=4, and extreme problems=5. The score for each dimension is combined into a 5-digit number that describes the patient's health status for analysis. |
| EuroQoL Visual Analogue Scale | A self-rated health status on a graduated (0–100) scale, with higher scores for higher HRQoL. The VAS is a quantitative measure of health outcome that reflect the patient's own judgement. |
| Physical function/activities of daily living (ADL) | |
| Barthel Index: BI | An ordinal scale (0–100) to measure functional independence and performance in the domains of personal care, mobility and ADL: Bowels, Bladder, Grooming, Toilet use, Feeding, Transfer, Mobility, Dressing, Stairs, Bathing. The BI is a quantitative measure with higher scores for higher functional independence and ADL. |
| Cognitive function | |
| Short Memory Questionnaire | A simple quantitative rating test for memory and cognitive disturbances consisting of a 14-item questionnaire. The result is shown as an ordinal scale (4–46) with higher scores for severe memory and cognitive disorders. |
| Mental health state | |
| Hospital Anxiety and Depression Scale: HADS | A quantitative questionnaire to assess psychiatric symptoms of anxiety and depression. The HADS is a 14-item questionnaire which includes 7-item subsets each for depression and anxiety. Each item is assigned a score between 0 and 3. Each 7-item subset for anxiety or depression is rated between 0 and 21. |
| Impact of Event Scale-Revised | A self-reported measure of post-traumatic stress disorder symptoms with 22 items including subscales for Intrusion (8 items), avoidance (8 items) and hyperarousal (6 items). Each item is rated on a 5-point scale ranging from 0 (not at all) to 4 (extreme), and the total score ranges from 0 to 88. |

ICU, intensive care unit.

## Baseline characteristics and treatment

The baseline characteristics of enrolled patients will be prospectively collected including age, height, weight, admission source, employment status before admission, presence of septic shock, source of infection, the results of bacterial cultures, Charlson comorbidity index, pre-existing comorbidities and BI before hospital admission, clinical frailty scale score, Acute Physiology And Chronic Health Evaluation II, Sequential Organ Failure Assessment score at ICU admission, maximum during ICU stay and at ICU discharge, and lactate level at ICU admission and maximum during ICU stay. The details of treatment during their ICU stay, which could influence outcomes, are also prospectively collected including surgical infection source control, use of neuromuscular blockade, analgesia, sedation agents, corticosteroids, vasopressors, non-invasive ventilation, mechanical ventilation,

extracorporeal membrane oxygenation, continuous or intermittent renal replacement treatment, use of a polymyxin-B immobilised column and hypoglycaemia/hyperglycaemic.

## Key data collection: implementation of the ABCDEF bundle and other supportive ICU care

The implementation rate for the entire ABDEF bundle and each individual element will be calculated by dividing the number of days when the entire bundle or each element is achieved according to the operational definitions of the ABCDEF bundle, by the total length of ICU stay. The operational definitions of the ABCDEF bundle are defined in several studies[29–31] and are listed in online supplemental table 2. The average consciousness level during the day or night based on Richmond Agitation-Sedation Scale,[32] the incidence and duration of delirium, the intensity of physical

**Table 2** Diagnostic definitions

| Variable | Definition |
|---|---|
| Postintensive care syndrome: PICS | If any of the following criteria are met; (1) physical impairment, (2) cognitive impairment, or (3) mental health disorders |
| Physical impairments | Score ≤90 in the Barthel Index (BI) |
| Cognitive impairments | Score <40 in the Short Memory Questionnaire |
| Mental health disorders | Presence of at least one of three psychiatric symptoms, including depression, anxiety or PTSD. The presence of anxiety is a score of 8 or higher in the subscale for anxiety of Hospital Anxiety and Depression Scale (HADS). The presence of depression is a score of 8 or higher in the subscale for depression of HADS. The presence of PTSD is a score of 25 or higher in the Impact of Event Scale-Revised (IES-R). |
| PICS-Family: PICS-F | Presence of mental health disorders is defined as the presence of at least one of three psychiatric symptoms, including depression, anxiety or PTSD. The presence of anxiety is a score of 8 or higher in the subscale for anxiety of Hospital Anxiety and Depression Scale (HADS). The presence of depression is a score of 8 or higher in the subscale for depression of HADS. The presence of PTSD is a score of 25 or higher in the IES-R. |

PTSD, post-traumatic stress disorder.

rehabilitation achieved during ICU stay and the time from ICU admission to achieve it, the implementation rate of element F (family engagement and empowerment, online), nutritional support including energy and protein per day within the first 14 days of their ICU stay and implementation of the ICU diary and use of physical restraints during the ICU stay will be collected prospectively.

## Outcomes

Primary outcomes include survival, which is the most important outcome of this study, and the incidence of PICS defined by the presence of any of the following: (1) physical impairment, (2) cognitive impairment or (3) mental health disorders at 12 months follow-up (table 2). Although this study will follow patients for up to 5 years after hospital discharge, long-term follow-up is subject to many patients dropping out of the study. Therefore, we primarily focus on outcomes at 12 months. Each incident of physical or cognitive impairment, or mental health disorders will be investigated according to predetermined definitions and cut-offs of the assessment tools shown in table 2. Secondary outcomes are the scores of assessments, such as EQ-5D-5L, EQ-VAS, BI, SMQ, HADS subset for anxiety or depression, and IES-R, employment status, weight loss or recovery after hospital discharge, rehospitalisation or readmission to an ICU, and the necessity to visit a Department of Emergency Medicine, Rehabilitation or Psychiatry. Data regarding the incidence of PICS-F defined as mental health disorders of the family after the patient's hospital discharge will be also collected (table 2). These outcomes will be followed up to 60 months (5 years) for additional analysis of long-term outcomes associated with sepsis.

## Statistical analysis

The sample size is calculated by the assumed survival rate at 12 months after hospital discharge. According to the assumption that the survival rate at 12 months is 75% with 95% CI width of 10%,[4 33 34] the calculated sample size needed is 289 patients. Considering approximately 20% lost to follow-up, a total of 362 patents is sufficient. Collecting a sample of this calculated size is considered feasible since each participating site should be able to enrol at least one patient per month based on the number of ICU patients admitted at each site in the past.

Primary and secondary outcomes will be descriptively analysed and presented as continuous variables with 95% CIs or numbers with a percentage. The association between outcomes and the implementation rate of the ABCDEF bundle will be analysed by a multivariate logistic or linear regression analysis. Covariates are selected from the background information of the hospital/ICU and the baseline characteristics that are clinically important and could have an influence on the outcomes based on previous studies. The survival analysis using the log-rank test or Cox-proportional hazard regression model with adjustment of baseline characteristics will also be performed creating a Kaplan-Meier Curve. Patients are divided into several groups based on the implementation rate of the ABCDEF bundle in the survival analysis.

Additional analyses using the same methods stated above with follow-up data at 36 or 60 months are planned to investigate changes in long-term outcomes of sepsis, focusing on survival and PICS/PICS-F over time.

In order to investigate the facilitating and hindering factors associated with implementation of the ABCDEF bundle, multivariable logistic regression analysis will be performed using background information for each hospital and ICU.

## Subset analyses

To conduct subset analyses, this study will include data not directly related to the primary analysis. For example,

urine samples on ICU days 3 and 5 will be collected to determine the concentration of TITIN, a muscle protein increasingly detected in urine when muscle is destroyed.[35] TITIN is suggested as a biomarker of ICU-acquired weakness and its association with long-term outcomes is unknown. Blood samples on ICU day 14 will be used to measure the serum albumin level, total lymph count and C reactive protein in blood to assess the presence of persistent inflammation, immunosuppression and catabolism syndrome[36] and its association with long-term outcomes of sepsis.

### Data management and follow-up

Patient inclusion and exclusion at the time of ICU admission and data collection will be carried out using an electronic data capture (EDC) system created exclusively for this study by a data management and clinical research support company (TXP Medical, Tokyo Japan).[37] Using the EDC system, each ICU can manipulate only data from their own ICU and cannot access data registered from other participating ICUs. Furthermore, the system alerts research collaborators whose patient data is lacking with alarms on the EDC dashboard to limit the amount of missing data. Only the principal investigator (KL) and ILOSS Study Committee members can monitor all patient data and ask research collaborators for data input according to the alert system. The database is protected by standard internet security and can be extracted only by the company with appropriate permission by the representative at each participating site which will be assessed by the principal investigator and the ILOSS Study Committee. The number of days after hospital discharge are shown in the EDC system and research collaborators at each participating site will receive an alert when the time for follow-up is approaching. To reduce loss to follow-up and facilitate data input, alerts will be sent to the research collaborators at regular intervals during the preset follow-up period. Lost to follow-up will be excluded from the primary analysis.

### Patient and public involvement

Patients and public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

### Ethics and dissemination

The study protocol was approved by the Ethics Committee of the Saiseikai Utsunomiya Hospital (No 2020-69), the central institution of this study, and all participating hospitals received ethical approval from local ethics committees before enrolling patients. The study is being conducted in accordance with the Declaration of Helsinki and the Ethical Policy published by Japanese Government.[38] Written informed consent is obtained from all patients or their designated representatives, such as close relatives, if the patient is unable to provide consent at the time of ICU admissions. The information regarding this study is shown in the website of the Japanese Association of Acute Medicine (in Japanese) (https://www.jaam.jp/info/2020/info-iloss_study.html). The results from this study will be disseminated through publications in peer-reviewed journals and presentations at scientific conferences in Japan or other countries.

## DISCUSSION

This is the first large-scale multicentre prospective cohort study to investigate survival and incidence of PICS and PICS-F in patients who recovered from sepsis up to 5 years after treatment. This study overcomes the limited nature of data currently available. This study will report the implementation of evidence-based ICU care which is strongly recommended to be incorporated into clinical practice in current guidelines. To date there are no reports on the actual implementation rates or the impact of implementation long-term outcomes. This study will report the association between long-term outcomes and implementation rates. This study identifies a potentially optimal implementation of evidence-based ICU care separate from disease-specific treatments to improve the long-term outcomes of patients with sepsis efficiently and effectively.

Due to the development of treatments for sepsis, such as the surviving sepsis campaign,[39] the short-term mortality of patients with sepsis has improved,[40] while the rate of patients who can return to their original lives at the same levels as before the septic event remains quite low.[41] PICS is regarded as the main barrier and a number of studies have shown that sepsis is a major risk factor for death and PICS after hospital discharge,[1–5 41] although existing data are limited and reflect only relatively short-term outcomes. Therefore, this study will provide valuable insights on sepsis-related long-term outcomes, focusing on survival and PICS which is expected to facilitate further research on ICU patients returning to their preseptic lives. This study evaluates long-term outcomes associated with PICS-F, mental health disorders of the family, which is broadly lacking in the current literature and should be investigated further to help families recover their lives as they were before the patients' ICU admission.

Evidence-based ICU care, such as the ABCDEF bundle and nutrition support is highly recommended.[12 18] Each modality of evidence-based ICU care improves the outcomes of ICU patients,[1 18 29 42] but the data are limited to during the hospital stay or through shortly after hospital discharge. If there is a strong association between long-term outcomes and performing evidence-based ICU care during the ICU stay, this cohort study will help to establish standards for the best ICU care and promote the further studies to investigate a causal relationship. It has been reported that there are several barriers to be overcome before initiating and performing evidence-based ICU care,[43] this study includes background information on the participating hospitals and ICUs which will identify facilitating and preventing factors associated with ICU administrative structures and policies.

This study will be meaningful not only for ICU staff, patients, and families, but also for policy-makers. Investigating early and late development of PICS and PICS-F are important reasons to provide specialised care during a critical illness such as sepsis.[44 45] Dysfunction after hospital discharge may result in increased overall healthcare expenditures for rehabilitation or follow-up and the probability of rehospitalisation or readmission to the ICU.[7–9 45] Therefore, the findings from this study will be helpful for policy-makers to sort out the best strategy for the use of scarce resources to reduce the total burden on patients and society.

We acknowledge several potential limitations of this study. The primary limitation will be lost to follow-up after hospital discharge. Lost to follow-up, which is excluded from the primary analysis, can cause large bias in outcomes. Furthermore, this study will reflect current practice and care in ICUs operating under common standardised guidelines for sepsis, while these findings are obtained only from participating sites in Japan and might be affected by the COVID-19 pandemic during their ICU stay. ICU policies, such as those related to infection control, ICU staffing, and restrictions on families will be subject to COVID-19-related policies and could have an unexpected influence on study outcomes. Lastly, we cannot adjust for unmeasured and unknown confounding factors and draw causal inferences because of the study design. However, we believe that this study will be a milestone orienting a future study to investigate causal inferences.

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