Ref: Ro J Neurol. 2022;21(4)
DOI: 10.37897/RJN.2022.4.3

The characteristics of the patients of Sepsis-associated encephalopathy (SAE) in Sanglah Central General Hospital's Emergency Room and Intensive Care Unit in the period from February 2019 to February 2022

Exaudi Caesario Parulian Sipahutar, I Wayan Widyantara

Department of Neurology, Sanglah General Hospital. Udayana University, Denpasar, Bali, Indonesia

ABSTRACT

Background and purpose. This study aimed to explain that Sepsis-Associated Encephalopathy (SAE) is a term that describes sepsis-associated brain dysfunction, which most often occurs in intensive care and is becoming an increasingly common disease in the Emergency Room with high rates of morbidity and mortality. In SAE, the clinical description that appears consists of a description of the underlying disease, namely sepsis, and encephalopathy. The source and aetiology of infection are essential factors in developing SAE.

Methods. It was a descriptive and retrospective study that described the characteristics of SAE patients. The data involved age, gender, vital signs, level of consciousness, haematological parameters, culture results, source of infection, underlying disease, and patient's external condition. The samples were taken based on the medical record data of patients who met the inclusion criteria, which were then processed descriptively through the number and percentage.

Results. There were 227 data in this study. The dominance of age ≥ 60 years was 56.32%, with a mortality rate of 61.73%. There were 157 patients with underlying disease of hypertension, and the most common source of infection was acute respiratory tract infection, with the most common microorganism involved Staphylococcus aureus.

Conclusions. Elderly patients show higher mortality in SAE, especially when the underlying disease is hypertension and stroke, with the most infections originating from the respiratory tract, so it often progresses more quickly and has a poor prognosis.

Keywords: encephalopathy, infection, sepsis-associated encephalopathy (SAE), *Staphylococcus aureus*

INTRODUCTION

Encephalopathy is a decrease in mental status or level of consciousness due to a disease process outside the brain. The word encephalopathy comes from the Greek "*en = inside*", "*kefahl = head*" and "*pauos = suffering*" [1]. Encephalopathy is a generalized metabolic disorder of neurons or glial cells, causing disturbances in consciousness, cognitive abilities, or behaviour. Encephalopathy can be caused by several factors, including infection, toxins, and metabolic and ischemic disorders. Acute encephalopathy is a condition in which brain function disturbances occur suddenly due to metabolic homeostasis problems or toxic substances [2]. Sepsis is an inflammatory process triggered by infection. Sepsis by severity is a spectrum of diseases from SIRS *(systemic inflammatory response syndrome)* to MODS *(multiple organ dysfunction syndromes)*. The CNS (central nervous system) involvement in sepsis causes encephalopathy and peripheral neuropathy [3].

Sepsis-associated encephalopathy (SAE) is a term that describes the brain dysfunction associated with sepsis. In the past, SAE was known as septic encephalopathy (SE). Some terms that also refer to the same condition are *septic-encephalitis, sepsis-induced en-*

Corresponding author:
Exaudi Caesario Parulian Sipahutar
E-mail: exaudycaesario@gmail.com

Article history:
Received: 13 October 2022
Accepted: 7 November 2022

cephalopathy, and *sepsis-associated delirium*. SAE is the most common form of encephalopathy in intensive care, with 50-70% of patients with sepsis. During the last few decades, sepsis-associated encephalopathy (SAE) has become an increasingly common disease in the Emergency Room (ER), with high morbidity and mortality rates. SAE is a common condition that significantly affects the outcome of sepsis. SAE is associated with a poor prognosis with a mortality rate of 16-63% [1].

The definition of sepsis emphasizes the body's response to infection-related disorders and organ dysfunction. Sepsis and its accompanying complications cause more deaths than prostate cancer, breast cancer, and HIV/AIDS, which place a significant financial burden on the health care system. Sepsis-associated encephalopathy (SAE) is a multifactorial syndrome characterized as diffuse cerebral dysfunction caused by a systemic response to infection without clinical or laboratory evidence of direct brain infection or other types of encephalopathy (e.g., hepatic or renal encephalopathy). The term Sepsis-associated encephalopathy is more appropriate than the term Septic encephalopathy," which is often defined as a consistent direct infection of the central nervous system [4]. Sepsis-associated encephalopathy is related to the body's ability to deal with infection from a complex pathophysiological response. Changes in the *Sequential Organ Failure Assessment* (SOFA score) score can identify a clinically uncontrolled inflammatory response and increase sepsis's diagnostic and therapeutic value. Sepsis-associated encephalopathy is one of the main manifestations of organ dysfunction in sepsis, which manifests in various forms; the main clinical features include slowing of mental activity, attention, impaired orientation, delirium, or coma [5]. A previous study showed that SAE has high morbidity and mortality rates and often causes long-term cognitive dysfunction, which affects the long-term quality of life [6].

METHODS

This research was descriptive with a retrospective study, namely the study described the characteristics of patients with sepsis-associated encephalopathy (SAE) in the Emergency Room and Intensive Care Unit of Sanglah Hospital in Denpasar, Bali during the period February 2019 to February 2022. The data collected was demographic data on the distribution of the study sample, including age, gender, and the patient's external condition, whether he was finally declared dead during hospitalization or managed to return home from hospital treatment regardless of discharge conditions. The underlying disease was a co-morbidity or particular medical condition that the patient had previously suffered or was acquired at the same time as the diagnosis of SAE. It had the potential to worsen the patient's outcome. The examination results included vital signs, level of consciousness, and haematological parameters that supported a state of infection, as well as culture results. The last thing to observe was the source of infection in patients, both those experienced by the patient entering the ER and those obtained by the patient during treatment at the hospital (intensive care). The research sample was taken based on the patient's medical record data, where all patients who met the inclusion criteria were included in this study. The number of samples was 277 patients. The inclusion criteria for the patients were as follows: (1) Diagnosis of sepsis: The patient was diagnosed with sepsis which is a life-threatening organ dysfunction caused by dysregulation of the host's response to infection; (2) Identification of SAE: Cognitive and neuropsychiatric disorders documented by the examining physician, with a Glasgow coma score (GCS) < 15 or manifestations of delirium (including inattention, disorientation, altered thought processes, decreased psychomotor activity, and agitation). The exclusion criteria were patients with sedative-associated cognitive effects, primary central nervous system disease (cerebrovascular disease, central nervous system infections, autoimmune encephalitis, seizures), metabolic encephalopathy (hypoglycemia, diabetic ketoacidosis, hepatic encephalopathy, pulmonary encephalopathy, uremic encephalopathy), and toxicosis. The data was then processed descriptively using the SPSS ver.25 program through the number and percentage.

All data involving human participants were approved by the Research Ethics Commission of Faculty of Medicine, Udayana University/Sanglah General Hospital. (number: JD-HG-2021-035). The written informed consent was waived due to the retrospective nature of this study. The results obtained in this study were reported according to the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) statement.

RESULTS

This study used a sample of patients with sepsis-associated encephalopathy (SAE) in the emergency room and intensive care unit at Sanglah Hospital, Denpasar, Bali, from February 2019 to February 2022. A total of 277 patients were included in this study. The characteristics of respondents assessed in this study included age, gender, vital signs, level of consciousness, haematological parameters, culture results, source of infection, underlying disease, and patient's external condition.

TABLE 1. The demographic data distribution of the research samples

1. Gender	**n (%)**
Male	150 (54,15 %)
Female	127 (45,85 %)
2. Age	
≥ 60	156 (56,32 %)
< 60	121 (43,68 %)
3. Mortality Rate (Patients' External Condition)	
Died	171 (61,73 %)
Return Home	106 (38, 27 %)
Total	**277 (100%)**

Table 1 shows the demographic distribution of the research sample. The highest gender was male, with as many as 150 patients (54.15%), while female as many as 127 patients (45.85%). Most of the age came from people over 60 years or equal to 60 years, with a total of 156 patients (56.32%) and the remaining 121 patients (43.68%) aged less than 60 years. The mortality rate (death) as a patient outcome condition was 171 patients (61.73%), and as many as 106 patients (38.27%) managed to return home from hospital treatment.

TABLE 2. The Frequency Distribution of the research subjects based on common illness

Common Illness	**Total**
Hypertension	157
Kidney disorders	76
Diabetes	53
CHF	18
COPD	4
Stroke	107
Parkinson's disease	20
Brain tumor	12
Brain infection	8

Table 2 shows the frequency distribution of research subjects based on their underlying disease. In general, the patients with the underlying disease were hypertension with 157 patients, followed by kidney disorders (76 patients), diabetes (53) patients, and COPD (4 patients). While the distribution of patients with underlying diseases in the field of neurology was the most, namely stroke with 107 patients, followed by Parkinson's disease (20 patients), brain tumors (12 patients), and brain infection (8 patients).

Based on the examination data obtained in this study (table 3), the patient was diagnosed as having an SAE condition based on the results of his physical and laboratory examination, which was investigated further by culture examination. It turned out that the most frequently involved microorganism was *Staphylococcus aureus* in 24 patients (8,66). %), *Escherichia coli* 15 patients (5.42%), *Acinetobacter baumannii* 5 patients (1.81%), *Pseudomonas aeruginosa* 4 patients (1.45%), *Klebsiella pneumonia* 4 patients (1.45%), *Streptococcus viridans* 3 patients (1.08%), *Candida albicans* 3 patients (1.08%), and several other microorganisms in rare numbers. In 91 patients (32.85%), no growth was found. However, it turned out that most of the patients did not undergo a culture test, namely 211 patients (76.17%), so it cannot be concluded that microorganisms may be involved in causing SAE in these patients.

TABLE 3. The characteristics of the respondents' individual examination results

1. Vital Sign	**n (%)**
Pulse: ≤ 90 times/minute	127 (45,85 %)
> 90 times/minute	150 (54,15 %)
Temperature:	
≤ 38˚C	226 (81,59 %)
> 38˚C	51 (18,41 %)
Respiration:	
≤ 20 times/minute	140 (50,54 %)
> 20 times/minute	137 (49,46 %)
GCS:	
15	28 (10,11 %)
< 15	249 (89,89 %)
2. Laboratory Results	
WBC: > 12.000/μL	225 (81,23 %)
≤ 12.000/μL	52 (18,77 %)
Platelets: < 100.000/mikroL	21 (7,59 %)
≥ 100.000/mikroL	256 (92,42 %)
3. Culture Test	
Staphylococcus aureus	24 (8,66 %)
Escherichia coli	15 (5,42 %)
Acinetobacter baumannii	5 (1,81 %)
Pseudomonas aeruginosa	4 (1,45 %)
Klebsiella pneumoniae	4 (1,45 %)
Streptococcus viridans	3 (1,08%)
Candida albicans	3 (1,08%)
Enterococcus faecium	2 (0,72 %)
Proteus mirabilis	1 (0,36 %)
Morganella morganii	1 (0,36 %)
Acinetobacter spp.	1 (0,36 %)
Bacillus sp.	1 (0,36 %)
Enterobacter cloacae	1 (0,36 %)
Streptococcus suis	1 (0,36 %)
No germ growth	91 (32,85 %)
Not checked	120 (43,32 %)
Total	**277 (100%)**

From the data, it was found that the occurrence of SAE conditions mostly came from infections in the respiratory tract, namely pneumonia. It was experienced by 153 patients (Table 4), which were divided into *human-acquired pneumonia* (HAP), *community-acquired pneumonia* (CAP), and *ventilator-acquired pneumonia* (VAP). The data showed that CAP had the most role in 85 patients (30.68%), followed by HAP

TABLE 4. The frequency distribution of the research subjects based on the source of infection

Source	n (%)
CAP	85 (30,68 %)
UTI	65 (23,47 %)
HAP	38 (13,72 %)
VAP	30 (10,83 %)
COVID-19	20 (7,22 %)
TBC	17 (6,14 %)
Decubitus ulcer	10 (3,61 %)
HIV	7 (2,53 %)
Abscess	3 (1,08 %)
Vasculitis	2 (0,72 %)
Total	**277 (100%)**

in 38 patients (13.72%) and VAP in 30 patients (10.83%). In comparison, the second most came from infections of the urinary tract (UTI) in as many as 65 patients (23.47%).

DISCUSSION

In SAE, the apparent clinical description consists of a description of the underlying disease, i.e., sepsis, and a clinical description of encephalopathy. The sepsis description can be SIRS, severe sepsis, septic shock, or multi-organ failure. SAE is a description of a generalized/diffuse disturbance of cerebral function. Brain dysfunction in SAE can include rapid deterioration of cortical function such as disorientation, delirium, confusion, cognitive impairment, memory impairment, and coma. In sepsis, symptoms of encephalopathy are not symptoms that occur due to high fever; encephalopathy does not improve with antipyretic treatment alone [7].

Sepsis is a clinical syndrome that complicates severe infection and is characterized by the cardinal signs of inflammation (vasodilation, leukocyte accumulation, and increased microvascular permeability) occurring in tissues distant from infection. Sepsis is one of the most common reasons for admission to a medical ICU and accounts for 37.4% of patient admissions [7]. *The American College of Chest Physicians and the Society of Critical Care Medicine* (ACCP/SCCM) held a consensus conference in 1991 to define sepsis and the syndrome associated with sepsis, which was modified in 2003, as shown below [8].

1. Systemic Inflammatory Response Syndrome. The systemic inflammatory response to various clinical disorders is manifested by two or more of the following conditions:

a. temperature <36˚C or > 38˚C
b. heart rate > 90 beats/minute
c. respiratory rate > 20 breaths/minute or PaCO2 < 32 mmHg
d. white blood cell (WBC) <4000 cells/μL, > 12,000 cells/μL, or > 10% immature (band form).

2. Infection. Infection is the invasion of normally sterile tissue by pathogenic organisms.

3. Bacteremia. Bacteremia is the presence of bacteria living in the blood.

4. Sepsis. Documented or suspected of any of the following:

a. General Parameters. Fever (core temperature > 38.3˚C), hypothermia (core temperature < 36˚C, heart rate > 90 bpm or > 2 SD above normal for age, tachypnea > 30 bpm, altered mental status, significant edema or balance positive fluid (> 20 mL/kg over 24 hours), and hyperglycemia (plasma glucose > 110 mg/dL or 7.7 mM/L) in the absence of diabetes.

b. Inflammation Parameters. Leukocytosis (white blood cell count > 12,000/μL), leukopenia (white blood cell count < 4,000/μL), normal white blood cell count with > 10% immature form, plasma C reactive protein > 2 SD above normal, and plasma procalcitonin > 2 SD above normal value.

c. Hemodynamic Parameters. Arterial hypotension (SBP < 90 mmHg systolic blood pressure, MAP < 70 mmHg, or decreased SBP > 40 mmHg in adults or less than two standard deviations below normal for age).

d. Organ Dysfunction Parameters. Arterial hypoxemia (PaO2/FiO2 < 300), acute oliguria (urine output 0.5 mg/dL or 44.2 micromol/L, coagulation abnormalities (INR 1.5 or aPTT > 60 seconds), ileus (no bowel sounds), thrombocytopenia (platelet count < 100,000/microL), and hyperbilirubinemia (total plasma bilirubin > 4 mg/dL).

e. Tissue Perfusion Parameters. Hyperlactataemia (> 1 mmol/L), decreased capillary refill, or mottling.

5. Severe Sepsis (Sepsis Syndrome). It is sepsis with complications of organ dysfunction. Thus, patients with sepsis with abnormal organ dysfunction parameters or tissue perfusion variables are classified as having severe sepsis.

6. Septic Shock. It is hypotension due to sepsis that persists despite adequate fluid resuscitation, which can be defined as an infusion of 30 mL/kg of crystalloid or requiring vasopressors to maintain a systolic blood pressure of 90 mmHg or a mean arterial pressure of 70 mmHg.

7. Multiple Organ Dysfunction Syndrome (MODS). It is progressive dysfunction of >1 organ in an acutely ill patient, so homeostasis cannot be maintained without intervention.

The source and etiology of infection are essential factors in the development of SAE, with bile duct or intestinal infections associated with a greater risk of SAE, followed by pulmonary infection. The most commonly implicated microorganisms are *Staphy-*

lococcus aureus, *Enterococcus faecium*, *Acinetobacter spp.*, *Pseudomonas aeruginosa*, and *Stenotrophomonas maltophilia* [9]. Patients with multiple bacteria on blood cultures and Candida albicans have more severe brain dysfunction and a higher mortality rate. While SAE is often described as an acute reversible syndrome, there is increasing evidence that SAE can pose a substantial risk for long-term cognitive impairment, including changes in mental processing speed, executive function, memory, attention, and visual-spatial abilities. These cognitive changes can last for several years even after recovery from sepsis and SAE and can affect functional ability, quality of life, and ability to return to work. It can be a tremendous burden on family members and caregivers. A recent study concluded that 70% of patients with sepsis had neurocognitive impairment at discharge from the hospital, and 45% had neurocognitive impairment within one year [10].

A complete physical examination to identify an occult source of infection (e.g., decubitus ulcer infection or other types of cellulitis or rash) should be accompanied by other appropriate investigations such as ultrasound, echocardiography, and CT scan. The use of culture (blood culture, respiratory or sputum culture, urine culture, and cerebrospinal fluid [CSF] analysis and culture) and appropriate serology to identify the organism responsible cannot be overlooked. The absence of bacteremia does not exclude SAE, and identifying the pathological organism is not always possible. Common reasons for difficulty in identifying disease-causing organisms are previous use of antibiotics, which may preclude detection of specific organisms or the presence of hidden abscesses [11].

A comprehensive metabolic analysis includes complete blood count, electrolyte levels (sodium, potassium, chloride, magnesium, phosphate, and calcium) and liver function (alanine and aspartate aminotransferase, alkaline phosphatase, and -glutamyltransferase), and renal function (serum creatinine) should be assessed to look for evidence of organ dysfunction or other abnormalities that may be contributing to sensorium changes. Several metabolic parameters may have good prognostic significance, and it is known that serum urea, creatinine, bilirubin, and alkaline phosphatase levels influence changes in direct proportion to the severity of encephalopathy. Any focal neurologic abnormality such as hemiparesis or cranial nerve abnormalities may suggest a focal neurologic process, such as an abscess or stroke, and require urgent neuroimaging [8].

Elderly patients show a higher risk of death from sepsis. A previous study by Chen et al. (2020) found that age was an independent risk factor for 28-day mortality in SAE patients. In addition, severely ill patients with the underlying disease often progress more rapidly and have a poor prognosis. Such patients may be more likely to develop central nervous system complications, especially when the underlying diseases are hypertension, diabetes, renal impairment, and chronic obstructive pulmonary disease (COPD) (table 2). The study also found that patients with sepsis with underlying hypertension had a higher risk of developing SAE. This study also showed that sepsis patients' underlying health status and severity were closely related to the occurrence of encephalopathy and poor outcomes in patients leading to death [12].

Most cases of sepsis and septic shock originate from the respiratory tract, namely, pneumonia, which is divided into *human-acquired pneumonia* (HAP), *community-acquired pneumonia* (CAP), and *ventilator-acquired pneumonia* (VAP). The same thing was found in this study, from 153 patients, it showed that CAP had the most role namely 85 patients (30.68%), followed by HAP in 38 patients (13.72%), and VAP in 30 patients (10.83%). This situation is caused because microorganisms more easily enter the body through inhalation or aspiration into the lung segments/lung lobes. Pneumonia infection can occur before entering the hospital, while receiving medical treatment, or during the treatment process in the intensive room. The incidence of nosocomial pneumonia (HAP) and VAP in the intensive care unit is more common, usually due to invasive measures given to patients in the form of an infusion, intubation, tracheostomy, and installation of a ventilator [13].

Tong et al. (2015) found that the mortality rate (76.1%) of stroke patients with SAE in the study was higher than in previous studies. Some findings may explain the difference. First, the severity of advanced brain injury may differ. For example, vasogenic edema in patients with SAE is more common than in those without SE. Second, the study showed that SOFA scores in the SAE group were significantly higher than in the non-SAE group, whereas previous studies have also shown that SAE deaths are almost always due to multiple organ failures. Third, the case study involved only severe SAE (all nosocomial coma). Therefore, the poor prognosis of stroke patients with SAE with nosocomial coma is more likely to be multifactorial, such as the severity of vasogenic edema, the presence of a high SOFA score, and other complications [14].

CONCLUSION

In this retrospective study, it was found that more than half of a sample of patients with sepsis-associated encephalopathy (SAE) who was estab-

lished based on the results of physical examination (vital signs and consciousness) and laboratory tests associated with the occurrence of the infectious process, was closely associated with poor outcome in these patients. Identified risk factors for SAE included older age (>= 60), underlying hypertension and stroke, and acute respiratory tract infection, with the most commonly involved microorganism being *Staphylococcus aureus* based on culture results.

Conflict of interest: none declared
Financial support: none declared

REFERENCES

1. Papadopoulos MC, Davies DC, Moss RF, Tighe D, Bennett ED. Pathophysiology of septic encephalopathy: a review. *Crit Care Med.* 2000 Aug;28(8):3019-24.
2. Bodensteiner JB. The evaluation of the hypotonic infant. *Semin Pediatr Neurol.* 2008 Mar;15(1):10-20.
3. Davies NW, Sharief MK, Howard RS. Infection-associated encephalopathies: their investigation, diagnosis, and treatment. *J Neurol.* 2006 Jul;253(7):833-45.
4. Iacobone E, Bailly-Salin J, Polito A, Friedman D, Stevens RD, Sharshar T. Sepsis-associated encephalopathy and its differential diagnosis. *Crit Care Med.* 2009 Oct;37(10 Suppl):S331-6.
5. Zampieri FG, Park M, Machado FS, Azevedo LC. Sepsis-associated encephalopathy: not just delirium. *Clinics* (Sao Paulo). 2011;66(10):1825-31.
6. Pandharipande PP, Girard TD, Jackson JC, Morandi A, Thompson JL, Pun BT, et al; BRAIN-ICU Study Investigators. Long-term cognitive impairment after critical illness. *N Engl J Med.* 2013 Oct 3;369(14):1306-16.
7. Vincent JL, Sakr Y, Sprung CL, Ranieri VM, Reinhart K, Gerlach H, et al; Sepsis Occurrence in Acutely Ill Patients Investigators. Sepsis in European intensive care units: results of the SOAP study. *Crit Care Med.* 2006 Feb;34(2):344-53.
8. Chaudhry N, Duggal AK. Sepsis Associated Encephalopathy. *Adv Med.* 2014;2014:762320.
9. Zhang LN, Wang XT, Ai YH, Guo QL, Huang L, Liu ZY, Yao B. Epidemiological features and risk factors of sepsis-associated encephalopathy in intensive care unit patients: 2008-2011. *Chin Med J* (Engl). 2012 Mar;125(5):828-31. PMID: 22490582.
10. Hopkins RO, Weaver LK, Chan KJ, Orme JF Jr. Quality of life, emotional, and cognitive function following acute respiratory distress syndrome. *J Int Neuropsychol Soc*. 2004 Nov;10(7):1005-17.
11. Gofton TE, Young GB. Sepsis-associated encephalopathy. *Nat Rev Neurol.* 2012 Oct;8(10):557-66.
12. Chen J, Shi X, Diao M, Jin G, Zhu Y, Hu W, Xi S. A retrospective study of sepsis-associated encephalopathy: epidemiology, clinical features and adverse outcomes. *BMC Emerg Med*. 2020 Oct 6;20(1):77.
13. Mulatu HA, Bayisa T, Worku Y, Lazarus JJ, Woldeyes E, Bacha D, et al. Prevalence and outcome of sepsis and septic shock in intensive care units in Addis Ababa, Ethiopia: A prospective observational study. *Afr J Emerg Med.* 2021 Mar;11(1):188-195.
14. Tong DM, Zhou YT, Wang GS, Chen XD, Yang TH. Early prediction and outcome of septic encephalopathy in acute stroke patients with nosocomial coma. *J Clin Med Res.* 2015 Jul;7(7):534-9.