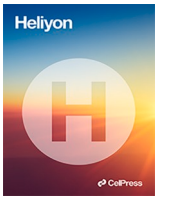
Heliyon 10 (2024) e29530

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

Clinical image of sepsis-associated encephalopathy midst *E. coli* urosepsis: Emergency department database study

Ewa Magdalena Sokołowska [a,*], Paweł Wityk [b], Jacek Szypenbejl [c], Rafael Petrosjan [a], Joanna Raczak-Gutknecht [b], Małgorzata Waszczuk-Jankowska [b], Danuta Dudzik [b], Michał Markuszewski [b], Mariusz Siemiński [c]

[a] *Emergency Department, University Clinical Center, Gdansk, Poland*
[b] *Department of Biopharmaceutics and Pharmacodynamics, Medical University of Gdańsk, Gdańsk, Poland*
[c] *Department of Emergency Medicine, Medical University of Gdansk, Poland*

A R T I C L E I N F O

Keywords:
Sepsis associated encephalopathy
Urosepsis
Escherichia coli
Mental alteration
APACHE

A B S T R A C T

Background: Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection, which, if untreated, leads to multi-organ failure. One of the severe possible complications is sepsis associated encephalopathy (SAE), a neurological dysfunction occurring secondary to a severe inflammatory response. It manifests as acute cognitive dysfunction and sudden-onset dysfunctions in mental state. Uropathogenic *Escherichia coli* is the most common pathogen causing bacteremia, responsible for 80% of uncomplicated outpatient urinary tract infections and 40% of nosocomial infections. The study aimed to assess the difference in the severity and the course of urosepsis caused by *E. coli* in patients with and without septic encephalopathy.

Materials and methods: This study presents a retrospective analysis of the population of urosepsis patients admitted to the Emergency Department between September 2019 and June 2022. Inflammatory parameters, urinalysis and blood cultures were performed, along with a clinical evaluation of sepsis severity and encephalopathy. The patients were then stratified into SAE and non-SAE groups based on neurological manifestations and compared according to the collected data.

Results: A total of 199 septic patients were included in the study. *E. coli*-induced urosepsis was diagnosed in 84 patients. In this group, SAE was diagnosed in 31 (36.9%) patients (33.3% in males, 40.5% females). Patients with SAE were found to be hypotensive ($p < 0{,}005$), with a higher respiratory rate ($p < 0{,}017$) resulting in a higher mortality rate ($p = 0.002$) compared to non-SAE septic patients. The APACHE II score was an independent risk factor associated with a higher mortality rate. Biochemical parameters between the groups did not show any statistical importance related to the severity of urosepsis.

Conclusions: The severity of urosepsis and risk of SAE development increase according to the clinical condition and underlying comorbidities. Urosepsis patients with SAE are at a higher risk of death. Patients should undergo more careful screening for the presence of SAE on admission, and more intense monitoring and treatment should be provided for patients with SAE. This study indicates the need to develop projects aiming to further investigate neuroprotective interventions in sepsis.

* Corresponding author.
E-mail address: ewa.sokolowska98@gumed.edu.pl (E.M. Sokołowska).

https://doi.org/10.1016/j.heliyon.2024.e29530
Received 6 October 2023; Received in revised form 8 April 2024; Accepted 9 April 2024
Available online 10 April 2024

1. Introduction

Sepsis represents a life-threatening organ dysfunction resulting from a dysregulated host response to infection, accounting for 6.4 % of Emergency Departments (ED) admissions and approximately 30 million hospitalizations

annually worldwide [1–3]. Out of these, 11 million in-hospital succumb to the condition [4]. These figures underscore the critical need for early recognition and improved management of sepsis, given its substantial long-term impact on a patient outcomes. Among the potential complications is sepsis associated encephalopathy (SAE), a neurological dysfunction arising secondary to a severe inflammatory reaction without direct involvement of the central nervous system (CNS) [5,6]. Sepsis-induced brain dysregulation may manifest as delirium, agitation, cognitive impairment, or coma, particularly among critically ill patients [6]. Notably, neurological symptoms may often precede the clinical manifestation of sepsis [7]. The diagnosis of SAE relies primarily on its clinical presentation and laboratory evidence confirming severe infection. Epidemiological data on SAE prevalence vary widely, ranging from 9 to 71% among in-hospital septic patients. This variability partly stems from the heterogeneity of the studied groups concerning sepsis localization and etiological factors. Approximately 70% of patients with confirmed bacteriemia exhibit neurological symptoms during the course of sepsis [3,8]. Despite ongoing exploration, the pathophysiology of SAE remains incompletely understood [9], underscoring the importance of thorough investigation into its epidemiology and etiology due to its significant impact on patient survival and potential long-term consequences of sepsis.

Urosepsis is clinically defined as severe urinary tract infection (UTI) characterized by features of severe inflammatory response syndrome (SIRS) [10].

The objectives of this study were to (a) assess the prevalence of SAE in a homogenous population of patients with urosepsis caused by *E. coli*; (b) demonstrate correlations between the presence of SAE and both clinical and laboratory findings in septic patients, such as the differences in APACHE II score and NRL values; (c) evaluate the association of SAE with mortality rates.

2. Methods and materials

2.1. Settings of the study

The study was conducted as a retroospective, observational, single-center, hospital-based cohort study. It enrolled patients suspected of sepsis who were admitted to the Clinical Emergency Department (ED) of tertiary care institute, namely the University Clinical Center in Gdańsk. The institute comprises a 1100-bed hospital and receives approximately 32 000 emergency admission annually, with an estimated 200 sepsis diagnoses made at the ED each year. The department is situated in a metropolitan area with a population of 1 000 000 and is one of four functioning emergency departments serving this region.

2.2. Patient recruitment/inclusion/exclusion criteria; Period of recruitment

The patient was diagnosed with sepsis according to Sepsis 3.0 definition. Urosepsis was identified based on positive cultures of both urine and blood samples for *E. coli.* Both were collected within the first hour of admission at ED and prior to the administration of the first dose of antibiotics. Patients with positive urine cultures were classified using the CDC National Healthcare Safety Network (NHSN) UTI case definitions. Sample collection was managed between September 2019 and June 2022.

Inclusion criteria

a. Patient presenting to the Emergency Department with suspected infection;
b. Patients aged ≥18 years old;
c. Presence of *E. coli* in urine and blood cultures, confirmed by a 48-h culture and genetic analysis;
d. Systemic Inflammatory Response Syndrome (SIRS) criteria met (≥2 of the following: respiratory rate >20/min or PaCO2 < 32 mmHg, heart rate >90 bpm, body temperature <36 °C or >38 °C, white blood cell count <4x10^9/L or >12x10^9/L, >10% immature neutrophils);
e. Acute onset cognitive impairment documented by medical staff;
f. Glasgow Coma Scale (GCS) score ≤15 points (reflecting a decrement of one point in the consciousness level).

Exclusion criteria

1. Sepsis other than urosepsis;
2. Primary central nervous system disease;
3. Urosepsis caused by pathogens other than *E. coli;*
4. Active chemotherapy and/or radiotherapy treatment for cancer;
5. Patients aged <18 year;
6. Lack of consent from a legal representative;
7. Pregnancy or lactation;
8. Hospital-acquired infection;
9. Antibiotic treatment within the past 2 weeks;

10. Insufficient reliable history to diagnose sudden neurological deterioration;
11. Central nervous system infection;
12. Hypoglycemia or hyponatremia.

Sepsis associated encephalopathy was defined as an acute decline in cognitive function, temporally related to the onset of sepsis symptoms [6].

Septic shock was defined as a severe sepsis with acute circulatory failure characterized by persistent hypotension (SBP $<$90 mm Hg, MAP $<$65 mm Hg or decrease in SBP by $>$ 40 mm Hg) despite adequate fluid resuscitation, necessitating the use of vasoconstrictive drugs [2].

3. Clinical assessment

Initially, patients underwent the evaluation at the Clinical Emergency Department, where a standard triage procedure based on Manchester Triage System was conducted for each admission. Triage involved assessing patient's vital signs, including heart rate, blood pressure, core body temperature, respiratory rate, blood oxygen saturation, and level of consciousness measured using the Glasgow Coma Scale. These measurements allowed for the quantification of the clinical criteria of Systemic Inflammatory Response Syndrome (SIRS).

In the study, cognitive impairment (manifesting as altered thinking, delirium or disorientation) was observed by medical staff (including nurses, doctors and paramedics). The evaluation was based on the neurological examination findings and a GCS score $\leq$15. When available, the neurological assessment was corroborated with information from relatives to ascertain whether any cognitive impairments were present before infection.

Clinical scales utilized in our study were employed to assess infection severity, patient mental state, and the risk of mortality associated with hospitalization.

1. **The Glasgow Coma Scale (GCS**) is employed as a quantitative measure to evaluate the level of consciousness in trauma and acute medical cases. The GCS score is derived from assessments of three responsiveness aspects: eye opening (4 points), verbal response (5 points), and motor response (6 points). The total score ranges from 3 to 15 points [11]. Presently, the scale finds widespread use in EDs and in ICUs for patient assessment. Its simplicity facilitates bedside application, proving to be a valuable tool for evaluating patent well-being in ICUs and providing a concise summary of overall severity.
2. **The Acute Physiology and Chronic Health Evaluation (APACHE) II** score serves as a severity-of-disease guidance tool, among several used in ICUs [12]. The integer score ranges from 0 to 71 points and is calculated using medical calculators based on various measurements and patient characteristics. Higher scores correlate with poorer outcomes and increased mortality among admitted patients. For the first time its role was validated to predict mortality in urosepsis by Sundaramoorthy et al. in a prospective observational study, employing it as a prognostic tool in urosepsis [12].
3. **The Neutrophil-to-Lymphocyte Ratio (NRL)** has emerged in research as a potential predictive factor for infection severity. It is an easily obtained and calculated complete blood count, which reflects the relationship between innate (neutrophils) and adaptive cellular immune responses (lymphocytes) during illness and other pathological states [13,14]. In healthy individuals, the mean NLR remains below 2, whereas during sepsis and septic shock, it rises to $>$10 and $>$ 20, respectively. Drăgoescu et al. found increased NRL in all septic patients, particularly in those with septic shock [15].

Within this patient cohort, we identified individuals who exhibited changes in mental status without a prior history of Central Nervous System (CNS) disorder.

4. Laboratory assessments

The blood and urine cultures underwent testing for the presence of *E. coli,* and only those that tested positive for E. coli were subsequently included in the study. Within this patient cohort, we identified individuals who exhibited altered mental status without a history of previous Central Nervous System (CNS) disorders complicated by cognitive chronic dysfunction.

Data were collected from all consecutive consenting patients enrolled in the study, including general information (age; gender; origin; comorbidities) and vital parameters assessed during triage. Additionally, medical histories was obtained before the blood sample collection. Comprehensive laboratory tests, including biochemical blood tests (serum creatinine level; aminotransferase levels; neutrophils count; white blood cell count (WBC, C-reactive protein (CRP); procalcitonin (PCT); sodium and potassium serum level; bilirubin; international normalized ratio (INR)) were performed on every patient.

Microbial test results provided information about the pathogen responsible for infection development, which was crucial for selecting patients diagnosed with urosepsis based on selective bacteremia. These results were then correlated with biochemical factors to differentiate patients with urosepsis from those with urinary tract infection (UTI). Relevant radiological investigations, such as abdomen and pelvic ultrasound, as well as computed tomographic (CT) scans, were performed as needed to further investigate the possible causes of urosepsis. Patients with acute mental alteration and no history of the neurocognitive disorders, underwent head CT scans to identify and rule out any acute life-threatening conditions.

Based on SIRS criteria and abnormal laboratory findings, patients received antibiotic treatment, primarily empirical cephalosporin or piperacillin-tazobactam. Patients were initially closely monitored within the Emergency Department unit and then transferred to

other departments or the ICU for further treatment, depending on the their clinical condition.

5. Statistical analysis

Continuous variables are presented as median along with interquartile range (IQR), while categorical variables are presented as percentages. Differences in continuous variables between independent groups were analyzed using JASP (version 0.16.4, 2018 the JASP team, the Netherlands). Mean, median and standard deviation were calculated, and the t-student test was also applied with corresponding p-values calculated. Categorical and quantitative variables are reported as numbers and medians (25th to 75th percentiles).

6. Ethical acceptance

The project concept was approved by the Bioethics Committee on 14 March 2019, by the Ethical Committee of the Medical University in Gdansk, prior to the initiation of the project (NKBBN/133/2019). All patients or their authorized representatives provided written informed consent to participate in the project. Informed consent was not required for the retrospective study design. All methods were conducted in accordance with relevant guidelines and regulations.

7. Results

Initially, 199 patients were included in the study. However, 115 patients were subsequently excluded, primarily due to alternative origins and etiologies of sepsis, accounting for 46,7% of cases. Additionally, 9,6% of patients suffered from chronic central nervous system disease, and 2,0% were under sedative effects, rendering clinical assessment unfeasible.

Following the exclusion of these patients, a total of 84 patients with urosepsis were screened and selected for both the SAE and non-SAE group. Based on in-hospital mortality outcomes, patients with SAE were further stratified into survival and non-survival groups, as shown at Fig. 1.

For sedated patients or those receiving ventilator-assisted breathing, their GCS scores were extracted before sedation. Patients for whom it was not possible to obtain accurate GCS scores prior to sedation were excluded from the study. We analyzed the clinical and laboratory outcomes of 84 patients, who met the inclusion criteria outlined in the Methods and Materials section.

Among these 84 patients, 31 patients (38.1%) were diagnosed with SAE (33.3% in males, 40.5% females). The median age of patients with SAE and those without was 74 (±14) and 70 (±17) years old, respectively. Although patients with SAE tended to be older, this difference was not statistically significant.

Patients with SAE during the course of urosepsis exhibited lower blood pressure values (median arterial pressure, $p < 0.005$) and higher respiratory rates ($p = 0.017$) compared to those without, as shown in Table 1. Additionally, a correlation between SAE and septic shock was observed ($p < 0.004$). Out of 31 patients from SAE group, 15 (48,4%) patients developed septic shock due to severe urinary tract infection, in contrast to only 2 patients in the non-SAE group.

In terms of inflammatory parameters, no statistical differences were found. PCT serum levels and white blood counts were higher in patients with SAE, but these differences were not statistically significant, ($p = 0.083$ and $p < 0,05$, respectively). The mean value of CRP was almost identical within both groups, as shown in Table 3. All patients were admitted to the Emergency Department due to suspicion of infection of unknown etiology. The patients selected for the study were diagnosed with urosepsis caused by *E. coli*.

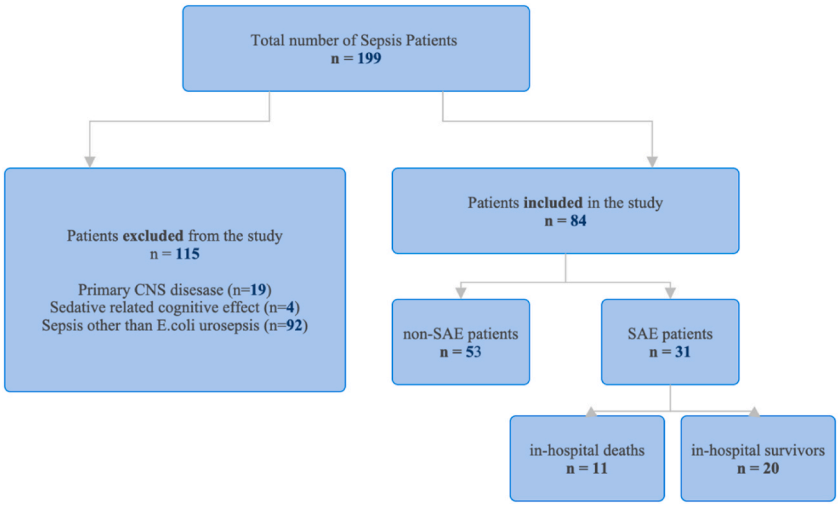


Fig. 1. Flowchart of patients.

Table 1
Mean Triage values.

Mean triage values	All patients	non-SAE patients	SAE patients	*p-value*
Body temperature (°C)	37,4 ± 1.9	37.5 ± 1.9	37.1 ± 1.8	*0.024*
Systolic blood pressure (mmHg)	114 ± 31	121 ± 27	103 ± 34	***0.015***
Diastolic blood pressure (mmHg)	67 ± 18	72 ± 16	60 ± 18	***0.003***
Mean arterial pressure (mmHg)	83 ± 21	88 ± 19	74 ± 22	***0.005***
Blood heart rate (bmp)	103 ± 21	106 ± 20	100 ± 22	*0.198*
Respiratory rate	19 ± 4	18 ± 3	20 ± 6	***0.017***

We observed significant differences regarding the APACHE II score ($p < 0.005$). Neutrophile-to-Lymphocyte (NRL) Ratios were of nonsignificant statistical importance ($p = 0.157$), as presented in Table 2.

The average length of hospitalization did not differ between the two groups of patients, in SAE cohort a mean equaled 231 ± 180 h, compared to 215 ± 118 h ($p = 0.613$) in septic patients. Females spent on average more time in the hospital than men.

In total, out of 84 patients, 12 patients died in the hospital, constituting 14,3% of patient population. Among these deceased patients, 11 were from the SAE cohort. Specifically, 7 women (22.6%) and 4 men (12.9%) died during hospitalization, whereas two of those patients passed away at the Emergency Department. In contrast, only one person from the non-SAE group died before being discharged. The difference in mortality rates between those two groups was statistically significant, with SAE patients being at a higher risk of death ($p = 0.002$).

We also assessed the incidence of underlying comorbidities and our analysis showed that SAE patients are more likely to suffer from chronic neurological disease (history of stroke, Alzheimer's and Parkinson's disease, dementia), hypertension and suffered from cancer than non-SAE patients, as presented in Table 4. The further assessment showed no correlation concerning severity of sepsis and underlying conditions. Within the SAE group 15 patients (48.4%) had acute kidney injury, characterized by higher creatinine level, although this finding did not reach statistical significance ($p = 0.085$).

8. Discussion

Sepsis-associated encephalopathy is a commonly encountered condition, albeit often overlooked [16]. The incidence of septic encephalopathy varies depending on the etiology of sepsis and the diagnostic criteria applied, which are not uniformly established. In our study, we employed criteria that involved assessing the patient's level of consciousness using the Glasgow Coma Scale, along with subjective assessment performed by medical staff. Additionally, we implemented comprehensive exclusion criteria to prevent overlap with patients suffering from chronic cognitive impairments, cerebrovascular diseases, or those under the influence of sedatives. However, for many chronically ill patients, family members reported a deterioration in verbal communication within 24 h preceding the onset of infection. Nevertheless, due to the potential unreliability of this information, such patients were excluded in our study. Nonetheless, the implementation of more specific criteria is warranted to enhance the accuracy of diagnosing acute-onset mental alterations. Research focusing on neuroimaging techniques (bedside electroencephalogram, craniocerebral ultrasound, magnetic resonance or computer tomography) should be considered to develop more objective indices for identifying SAE [17]. It can provide valuable insights into the structural and functional changes in the brain associated with SAE. While bedside electroencephalogram (EEG) and craniocerebral ultrasound are more accessible and feasible in the acute care setting, MRI offers a more comprehensive evaluation of brain structure and function. Imaging studies using MRI and CT have demonstrated changes in the brains of patients with SAE that are also seen in disorders such as stroke [18](19). Therefore, including this imaging technique would indeed, enhance the diagnostic capabilities for SAE. Beyond neuroprotective markers, exploring markers of neuronal injury is indeed crucial for understanding the pathophysiology and prognosis of SAE. Markers such as neuron-specific enolase (NSE), S100B protein, as well as glial fibrillary acidic protein (GFAP) can provide valuable information about neuronal damage and astroglial activation in SAE [19]. Therefore, it is essential to broaden the scope of biomarkers considered in SAE research to encompass markers of neuronal injury alongside neuroprotective markers. Incorporating MRI studies alongside bedside techniques like EEG and craniocerebral ultrasound can offer a more comprehensive assessment of SAE-related brain abnormalities.

The homogeneity of the population in our study holds significant importance. Patients presenting with urosepsis to the Emergency Departments (ED) exhibit heterogeneous signs and symptoms, particularly in elderly individuals where typical UTI symptoms such as dysuria and polyuria may not be present. Clinical features, aligned in one study for suspected UTI include (i) mental alteration (ii), changes in behavior (iii), urine abnormalities, and (iv) fever or chills. These findings suggest a combination of specific and non-specific UTI symptoms that should be considered when assessing UTI in elderly people [20,21]. Other research, has focused on the correlation between clinical aspects and SAE itself. For instance, in the study of Chen et al. a significant increase in gastrointestinal infection and

Table 2
Assessment of clinical scales.

Scales	All patients	non-SAE patients	SAE patients	*p-value*
Neutrophiles-to-lymphocyte ratio (NRL)	24.57 ± 22.19	21.87 ± 16.84	29.17 ± 28.91	*0.157*
Glasgow Coma Scale	14 ± 1	15 ± 0	12 ± 3	***<0.001***
APACHE II Score	16.6 ± 6.3	14 ± 5	20 ± 6	***0.004***

Table 3
Laboratory parameters on the admission to the Emergency Department.

Laboratory parameters	Mean laboratory values			
	all patients	non-SAE patients	SAE-patients	*p-value*
C-reactive protein (CRP) (mg/dL)	191.0 ± 115.0	185.70 ± 118.91	200.01 ± 109.29	*0.580*
Procalcitonin (PCT) (mg/dL)	31.17 ± 70.12	18.38 ± 38.04	52.78 ± 101.34	*0.083*
Creatinine (mg/dL)	2.42 ± 2.06	2.11 ± 1.91	2.94 ± 2.23	*0.085*
Sodium serum (mmol/L)	136.00 ± 5.62	136.09 ± 4.25	135.58 ± 7.48	*0.685*
Potassium serum (mmol/L)	4.28 ± 0.98	4.26 ± 0.67	4.32 ± 1.37	*0.758*
White blood cell count	14.5 6 ± 8.47	13.06 ± 5.25	17.1 ± 11.82	*0.048*
Aspartate aminotransferase (IU/L)	50.96 ± 62.90	36.00 ± 25.50	73.79 ± 91.70	*0.080*
Alanine aminotransferase (IU/L)	41.21 ± 48.17	33.06 ± 38.04	51.96 ± 58.05	*0.159*
Lactates (mmol/L)	3.38 ± 3.25	2.93 ± 2.41	3.82 ± 3.92	*0.343*
Neutrofile count	13.71 ± 11.47	11.62 ± 4.82	17.30 ± 17.40	*0.062*
Lymphocytes count	1.11 ± 1.84	0.82 ± 0.53	2.90 ± 0.12	*0.117*
Prothrombin time (INR)	3.52 ± 17.49	1.13 ± 0.48	7.44 ± 28.33	*0.114*
Bilirubine (mg/dL)	2.09 ± 4.57	1.05 ± 0.87	3.73 ± 7.05	*0.184*

Table 4
Comorbidities of SAE and non-SAE patients.

Disease/cohort group	SAE patients	non-SAE patients
Diabetes mellitus	12/31 (0.39)	28/53 (0.53)
Hypertension	18/31 (0.58)	17/53 (0.32)
Chronic obturatory pulmonary disease	2/31 (0.06)	4/53 (0.08)
Cardiac failure	4/31 (0.13)	12/53 (0.23)
Neoplasm history	5/31 (0.16)	5/53 (0.09)
Chronic renal failure	5/31 (0.16)	8/53 (0.15)
Acute kidney injury	15/31 (0.48)	22/53 (0.41)

detection of Enterococcus in patients with SAE was observed, suggesting the potential influence of gut microbiota in the pathogenesis of SAE [22]. Further research has demonstrated a close relationship between gut microbiota and the central nervous system, highlighting its impact on the development of neurological complications [23,24].

In our research, the study group was limited to patients diagnosed with *E. coli* urosepsis, exclusively. To the best of our knowledge, there is no specific data on SAE within the population of patients with urosepsis caused by *E. coli*, rending this research a valuable observation. Previous studies have demonstrated a significant discrepancy in the occurrence of SAE among patients with sepsis. For instance, in the study by Chen J. et. all [22], the group of patients with SAE was reported to be 43.6%, while Lina Zhang et al. [25]. determined the prevalence of SAE at 17.7%. In our study, out of 84 patients meeting the diagnostic criteria for urosepsis, 31 patients (36.9%) exhibited symptoms of encephalopathy, ranging from cognitive impairment to decreased consciousness, delirium and coma. These symptoms are likely attributable to diffuse brain dysfunction resulting from a severe systemic reaction. The exact mechanism is not yet fully understood. While multiple mechanisms contribute to SAE, recent studies suggest that microvascular dysfunction of nerve cells and disruption of the blood-brain barrier (BBB) play pivotal roles in its pathogenesis [6,26,27]. Microvascular dysfunction can lead to impaired cerebral perfusion, resulting in cerebral hypoperfusion and ischemia, which contribute to neuronal dysfunction and injury. Additionally, compromised integrity of BBB allows the infiltration of inflammatory mediators and circulating pathogens into the brain parenchyma, triggering neuroinflammation and oxidative stress. The inflammatory milieu promotes the generation of harmful free radicals, exacerbating neuronal damage and ultimately leading to neuronal apoptosis.

In our study, we assessed the rate of death during hospitalization, without conducting a long-term assessment. The mortality rate during the hospital stay in patients with SAE was 35.5%, while it was 1.8% in the group of patients without SAE. Previous studies have consistently demonstrated that SAE is associated with high morbidity and mortality. For instance, Sonneville R. et al. [22] indicated that the 28-day and 180-day mortality rates among SAE patients were 45.95% and 55.41%, respectively, while in a study by Jiayi Chen et al. [28] the 28-day mortality rate was 42.5%. In contrast, the authors of Chen et al. paper observed no correlation between SAE and length of hospitalization, suggesting that septic encephalopathy may significantly influence long-term treatment outcomes and the quality of social functioning, instead. However, the authors indicate that the choice of hospital length of stay may result in statistical bias, due to the critical condition of patients leading to death in the early phase of treatment. Similarly to Chen et al., results, SAE increased risk of mortality in our population. Simultaneously, patients with SAE had higher score on APACHE II. Therefore, we find that our results stay in line with observations of Chen et al. Furthermore, the authors implied that patients manifesting SAE are more susceptible to developing complications of the central nervous system progressively after discharge [29,30]. That may lead to potential long-term cognitive dysfunction including decrease in mental-processing speed, memory, and attention capabilities [31].

Deterioration of the general condition in the course of sepsis is one of the most common reasons for admission to Emergency Departments. In the clinical center where the study was conducted, urosepsis is diagnosed in approximately 200 patients per year. In the general population 25% of urogenital infections (UTIs) are complicated by sepsis [32,33]. Urinary tract infection is the most frequently diagnosed infection in the population of long-term care residents at nursing homes, second only to respiratory tract

infections and it predominantly affects woman [34]. As the population ages, the number of UTIs in elderly patients is expected to increase. We did not observe any difference in the mean age of patient with and without SAE. Nevertheless, the median age of patients with SAE was 74 ± 14. It is well-established that SAE more commonly affects elderly individuals (aged >65 years) with significant concomitant comorbidities such as hypertension, chronic heart failure, chronic kid ney disease, immunocompromised status, post-surgical conditions, or patients with altered mental state [35,36]. General practitioners should remain vigilant when treating patients with positive bacterial urinalysis and acute mental state abnormalities, considering that neurological manifestations may emerge before infectious symptoms.

We also assessed the incidence of underlying comorbidities. Our analysis showed that SAE patients are more likely to suffer from hypertension and had undergone oncological treatment (Table 2). Hypertension is also a risk factor for cerebrovascular diseases such as stroke and small vessel disease, which can result in cognitive impairment and contribute to the development or exacerbation of SAE. Chronic hypertension may predispose individuals to conditions such as hypertensive encephalopathy, characterized by altered mental status and cerebral edema, which can resemble features of SAE. Cancer and its treatments, including chemotherapy and radiation therapy, can have direct and indirect effects on the CNS, leading to cognitive dysfunction, may induce neurotoxicity, neuro-inflammation, demyelination as well as disruption of the blood-brain barrier. Cancer-related factors such as immune dysfunction, tumor burden, and paraneoplastic syndromes may also play a role in the pathogenesis of SAE. Further assessment of other potential comorbidities, revealed no correlation between the severity of sepsis and underlying conditions. A recent study demonstrated a relationship between chronic obstructive pulmonary disease (COPD) and SAE, but we did not observe a similar connection in our research [28]. The disruption of the blood-brain-barrier may be attributed to various conditions, one of which could be hypertension and a history of stroke, commonly observed in patients with SAE [37]. Hypertension and associated metabolic disturbances may constitute significant susceptibility factors for cognitive alterations and, consequently, risk factors for developing SAE. Understanding these associations can help clinicians identify high-risk patients, implement preventive measures, and tailor management strategies to optimize outcomes in SAE.

We found that within the SAE group 15 patients (48.4%) had acute kidney injury (AKI), manifested by an increase in serum creatinine concentration and/or a decrease in urine output. However, statistically, we did not observe a significant difference between non-SAE and SAE patients. Nevertheless, the intense fluid resuscitation and diuretic treatment may attenuate the increase in serum creatinine level, making the diagnosis of this condition difficult and sometimes delayed. Globally, there is a growing incidence of sepsis-associated acute kidney injuries, currently ranging between 40 and 50% in the ICU [38]. It remains a major complication of sepsis among critically ill patients, associated with a poorer prognosis and increased morbidity [39].

Furthermore, we found that APACHE II score is associated with a higher mortality rate ($p = 0.002$) among *E. coli* urosepsis patients with SAE. The incidence of *E. coli* urosepsis complicated by SAE is associated with a poorer prognosis and worse outcomes. In our research the APACHE II score has been used as a predictor of increased mortality among SAE patients, highlighting the importance of general health condition and its correlation with the severity of sepsis. Both factors are closely related to the prevalence of encephalopathy. Our results are consistent with observations in recent research on sepsis-associated brain injury [6,22,40]. It is worth emphasizing that a GCS score <15 was required to classify a patient as having SAE, meanwhile the GCS score is also a component of the APACHE II score. This may introduce potential bias.

The laboratory findings did not correlate significantly with the severity of urosepsis. Procalcitonin (PCT) serum levels and white blood cell counts were higher among SAE patients ($p = 0.083$; $p < 0,05$ respectively). Although, PCT levels were noticeably higher in SAE patients, the difference was not statistically significant and should be interpreted as a marker of general inflammatory reaction. The mean C-reactive protein (CRP) value was almost identical between the two groups. Our inability to demonstrate a significant correlation between laboratory findings and the occurrence of SAE in urosepsis patients may be attributed to the small sample size. Recent studies, have suggested a correlation between higher PCT serum concentrations, lower platelet counts, and SAE detection, but these studies involved larger population [21]. Meta-analyses on larger cohorts are warranted to further assess those correlations.

Patients with SAE in the course of urosepsis had lower blood pressure values (median arterial pressure ($p < 0.005$), systolic blood pressure ($p < 0.015$)) and presented with higher respiratory rate ($p = 0.017$). Zhao et al. [40] claim that certain hemodynamic parameters may decrease the incidence of SAE and the 28-day mortality in patients with SAE. Meanwhile, Young G.B. et al. [6] found that certain patients with sepsis may experience brain dysregulation despite adequate hemodynamics of the microcirculation, which is consistent with the observations of our patients.

9. Conclusions

Patients suffering from SEA are at a higher risk of mortality. All patients with altered mental status upon the admission to the hospital showed improvement and were verbally responsive upon discharge. However, changes in cognitive abilities may persist for years after recovery from sepsis, leading to a decline in quality of life, impairing social activities, and disrupting daily functioning. Studies have demonstrated that up to 70% of sepsis survivors who experienced neurological complications exhibit long-lasting neurological impairments, including mood alterations, cognition and motor functioning [41,42]. It places a burden on both family members and caregivers. Further understanding of the various clinical manifestations of sepsis is needed in order to improve the effectiveness of clinical interventions and care quality, as prompt control appears to be crucial in preventing increased mortality in severely encephalopathic patients.

Informed consent statement

The requirement for informed consent was waived because of the retrospective nature of the study.

Limitations of the study research

Inevitably, our study presents some limitations [1]: our failure to detect any significant differences concerning laboratory findings in the present study may be attributable to our relatively small sample size; this limitation results from very strict selection criteria, as our main focus was on the homogenous population of urosepsis patients [2]; a significant limitation of multiple retrospective study is the lack of standardized, validated, globally accepted diagnostic criteria for SAE, despite using the definition of SAE with reference to previous high-quality retrospective studies on SAE, this may lead to the inaccurate segregation of the two groups of patients; the reliability of diagnostic criteria for Sepsis-associated Encephalopathy (SAE) patients and inclusion criteria can vary depending on several factors, including the specificity and sensitivity of the criteria, the context in which they are applied, and the experience of the medical staff conducting the assessments [3]; this is a single-centered, retrospective study.

The strength of our study lies in the selection of patients, specifically *E. coli* urosepsis patients with SAE, which have been selected. To the best of our knowledge, no research of this homogeneity has been performed before. The narrow selection of patients may highlight to clinicians the importance of observing dynamic changes and not dismissing neurological symptoms in patients with infection.

Data availability statement

The complete data that support the findings of this study are available on request from the corresponding author.

CRediT authorship contribution statement

Ewa Magdalena Sokołowska: Writing – original draft, Visualization, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Paweł Wityk:** Writing – review & editing, Software, Formal analysis, Conceptualization. **Jacek Szypenbejl:** Project administration, Methodology, Investigation, Conceptualization. **Rafael Petrosjan:** Investigation, Data curation. **Joanna Raczak-Gutknecht:** Writing – review & editing, Project administration, Conceptualization. **Małgorzata Waszczuk-Jankowska:** Software, Formal analysis. **Danuta Dudzik:** Formal analysis. **Michał Markuszewski:** Writing – review & editing, Validation, Resources, Funding acquisition. **Mariusz Siemiński:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Michal Markuszewski reports financial support was provided by National Science Centre Poland. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] E. Rezende, J.M. Silva, A.M. Isola, E.V. Campos, C.P. Amendola, S.L. Almeida, Epidemiology of severe sepsis in the emergency department and difficulties in the initial assistance, Clinics 63 (4) (2008 Aug) 457–464.
[2] M. Shankar-Hari, G.S. Phillips, M.L. Levy, C.W. Seymour, V.X. Liu, C.S. Deutschman, et al., Developing a new definition and assessing new clinical criteria for septic shock: for the third international consensus definitions for sepsis and septic shock (Sepsis-3), JAMA 315 (8) (2016 Feb 23) 775–787.
[3] C. Rhee, R. Dantes, L. Epstein, D.J. Murphy, C.W. Seymour, T.J. Iwashyna, et al., Incidence and trends of sepsis in US hospitals using clinical vs claims data, 2009-2014, JAMA 318 (13) (2017 Oct 3) 1241–1249.
[4] S.C. Tauber, M. Djukic, J. Gossner, H. Eiffert, W. Brück, R. Nau, Sepsis-associated encephalopathy and septic encephalitis: an update [Internet], Expert Rev. Anti-infect. Ther. 19 (2) (2021) 215–231. Feb 1 [cited 2022 May 11], https://www.tandfonline.com/doi/full/10.1080/14787210.2020.1812384.
[5] L. Zhao, Y. Wang, Z. Ge, H. Zhu, Y. Li, Mechanical learning for prediction of sepsis-associated encephalopathy, Front. Comput. Neurosci. 15 (2021) 739265.
[6] T.E. Gofton, G.B. Young, Sepsis-associated encephalopathy, Nat. Rev. Neurol. 8 (10) (2012 Oct) 557–566.
[7] C.F. Bolton, G.B. Young, D.W. Zochodne, The neurological complications of sepsis, Ann. Neurol. 33 (1) (1993 Jan) 94–100.
[8] M. Gu, X.L. Mei, Y.N. Zhao, Sepsis and cerebral dysfunction: BBB damage, neuroinflammation, oxidative stress, apoptosis and autophagy as key mediators and the potential therapeutic approaches, Neurotox. Res. 39 (2) (2021 Apr) 489–503.
[9] C. Ren, R.Q. Yao, H. Zhang, Y.W. Feng, Y.M. Yao, Sepsis-associated encephalopathy: a vicious cycle of immunosuppression, J. Neuroinflammation 17 (1) (2020 Jan 10) 14.
[10] P.F. Czempik, M.P. Pluta, Ł.J. Krzych, Sepsis-associated brain dysfunction: a review of current literature, Int. J. Environ. Res. Publ. Health 17 (16) (2020 Aug 12) 5852.
[11] S. Jain, L.M. Iverson, Glasgow coma scale, in: StatPearls [Internet], StatPearls Publishing, Treasure Island (FL), 2022 [cited 2023 Feb 20]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK513298/.
[12] S. VijayGanapathy, ViS. Karthikeyan, J. Sreenivas, A. Mallya, R. Keshavamurthy, Validation of Apache II scoring system at 24 hours after admission as a prognostic tool in urosepsis: a prospective observational study, Investig Clin Urol 58 (6) (2017 Nov) 453–459.
[13] S. Spoto, D.M. Lupoi, E. Valeriani, M. Fogolari, L. Locorriere, G. Beretta Anguissola, et al., Diagnostic accuracy and prognostic value of neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios in septic patients outside the intensive care unit, Medicina (Kaunas) 57 (8) (2021 Aug 7) 811.

[14] J. Jiang, R. Liu, X. Yu, R. Yang, H. Xu, Z. Mao, et al., The neutrophil-lymphocyte count ratio as a diagnostic marker for bacteraemia: a systematic review and meta-analysis, Am. J. Emerg. Med. 37 (8) (2019 Aug) 1482–1489.
[15] A.N. Drăgoescu, V. Pădureanu, A.D. Stănculescu, L.C. Chiuțu, P. Tomescu, C. Georgmăneanu, et al., Neutrophil to lymphocyte ratio (NLR)—a useful tool for the prognosis of sepsis in the ICU [Internet], Biomedicines 10 (1) (2021) 75. Dec 30 [cited 2023 Feb 13], https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8772781/.
[16] T. Zhao, Y. Xia, D. Wang, L. Pang, Association between elevated serum tau protein level and sepsis-associated encephalopathy in patients with severe sepsis, 2019 Jul 17 [cited 2023 Feb 13], Can J Infect Dis Med Microbiol [Internet] (2019) 1876174. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6664571/.
[17] N.D. Pantzaris, C. Platanaki, K. Tsiotsios, I. Koniari, D. Velissaris, The use of electroencephalography in patients with sepsis: a review of the literature, J Transl Int Med 9 (1) (2021 Mar) 12–16.
[18] D.J. Stubbs, A.K. Yamamoto, D.K. Menon, Imaging in sepsis-associated encephalopathy–insights and opportunities, Nat. Rev. Neurol. 9 (10) (2013 Oct) 551–561.
[19] S. Schütze, D.A. Drevets, S.C. Tauber, R. Nau, Septic encephalopathy in the elderly – biomarkers of potential clinical utility [Internet], Front. Cell. Neurosci. 17 (2023) [cited 2024 Mar 11];. Available from: https://www.frontiersin.org/articles/10.3389/fncel.2023.1238149.
[20] T.A. Rowe, M. Juthani-Mehta, Urinary tract infection in older adults [Internet], Aging Health 9 (5) (2013), https://doi.org/10.2217/ahe.13.38. Oct [cited 2023 Feb 20], https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3878051/.
[21] M. Gajdács, M. Ábrók, A. Lázár, K. Burián, Urinary tract infections in elderly patients: a 10-year study on their epidemiology and antibiotic resistance based on the WHO access, watch, reserve (AWaRe) classification, Antibiotics (Basel) 10 (9) (2021 Sep 11) 1098.
[22] J. Chen, X. Shi, M. Diao, G. Jin, Y. Zhu, W. Hu, et al., A retrospective study of sepsis-associated encephalopathy: epidemiology, clinical features and adverse outcomes [Internet], BMC Emerg. Med. 20 (1) (2020) 77, https://doi.org/10.1186/s12873-020-00374-3. Oct 6 [cited 2023 Feb 9].
[23] H. Liao, H. Li, Y. Si, H. Bao, [Research progress of sepsis associated encephalopathy influenced by gut microbiota via efferocytosis], Zhonghua Wei Zhong Bing Ji Jiu Yi Xue 34 (2) (2022 Feb) 194–197.
[24] S. Li, J. Lv, J. Li, Z. Zhao, H. Guo, Y. Zhang, et al., Intestinal microbiota impact sepsis associated encephalopathy via the vagus nerve, Neurosci. Lett. 662 (2018 Jan 1) 98–104.
[25] L na Zhang, X ting Wang, Ai Y. hang, Guo Q. lian, L. Huang, Z yong Liu, et al., Epidemiological features and risk factors of sepsis-associated encephalopathy in intensive care unit patients: 2008-2011, Chin Med J (Engl). 125 (5) (2012 Mar) 828–831.
[26] N. Chaudhry, A.K. Duggal, Sepsis associated encephalopathy, Adv. Met. Med. 2014 (2014) 762320.
[27] J. Wang, Q. Zhu, Y. Wang, J. Peng, L. Shao, X. Li, Irisin protects against sepsis-associated encephalopathy by suppressing ferroptosis via activation of the Nrf2/GPX4 signal axis, Free Radic. Biol. Med. 187 (2022 Jul) 171–184.
[28] G. Jin, S. Wang, J. Chen, W. Hu, Y. Zhu, S. Xi, Identification of sepsis-associated encephalopathy risk factors in elderly patients: a retrospective observational cohort study, Turk. J. Med. Sci. 52 (5) (2022 Oct) 1513–1522.
[29] N.K. Manjappachar, J.A. Cuenca, C.M. Ramírez, M. Hernandez, P. Martin, M.P. Reyes, et al., Outcomes and predictors of 28-day mortality in patients with hematologic malignancies and septic shock defined by sepsis-3 criteria, J Natl Compr Canc Netw 20 (1) (2022 Jan) 45–53.
[30] C.L. Sprung, P.N. Peduzzi, C.H. Shatney, R.M. Schein, M.F. Wilson, J.N. Sheagren, et al., Impact of encephalopathy on mortality in the sepsis syndrome. The veterans administration systemic sepsis cooperative study group, Crit. Care Med. 18 (8) (1990 Aug) 801–806.
[31] T.J. Iwashyna, E.W. Ely, D.M. Smith, K.M. Langa, Long-term cognitive impairment and functional disability among survivors of severe sepsis, JAMA 304 (16) (2010 Oct 27) 1787–1794.
[32] A. Porat, B.S. Bhutta, S. Kesler, Urosepsis, in: StatPearls [Internet], StatPearls Publishing, Treasure Island (FL), 2022 [cited 2023 Feb 20]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK482344/.
[33] N. Petrosillo, G. Granata, B. Boyle, M.M. Doyle, B. Pinchera, F. Taglietti, Preventing sepsis development in complicated urinary tract infections, Expert Rev. Anti Infect. Ther. 18 (1) (2020 Jan) 47–61.
[34] M.E. Hibbing, M.S. Conover, S.J. Hultgren, The unexplored relationship between the urinary tract infections and the autonomic nervous system [Internet], Auton. Neurosci. 200 (2016 Oct) 29–34 [cited 2023 Feb 9], https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4670803/.
[35] Hypertension Is Related to Cognitive Impairment | Hypertension [Internet]. [cited 2023 Feb 20]. 31(3): 780–786. Available from: https://www.ahajournals.org/doi/10.1161/01.HYP.31.3.780.
[36] R. Sonneville, E. de Montmollin, J. Poujade, M. Garrouste-Orgeas, B. Souweine, M. Darmon, et al., Potentially modifiable factors contributing to sepsis-associated encephalopathy, Intensive Care Med [Internet] 43 (8) (2017) 1075–1084, https://doi.org/10.1007/s00134-017-4807-z. Aug 1 [cited 2023 Feb 20].
[37] L. Kilander, H. Nyman, M. Boberg, L. Hansson, H. Lithell, Hypertension is related to cognitive impairment: a 20-year follow-up of 999 men, Hypertension 31 (3) (1998 Mar) 780–786.
[38] S. Peerapornratana, C.L. Manrique-Caballero, H. Gómez, J.A. Kellum, Acute kidney injury from sepsis: current concepts, epidemiology, pathophysiology, prevention and treatment [Internet], Kidney Int. 96 (5) (2019 Nov) 1083–1099 [cited 2023 Feb 20], https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6920048/.
[39] R.L. Mehta, J. Bouchard, S.B. Soroko, T.A. Ikizler, E.P. Paganini, G.M. Chertow, et al., Sepsis as a cause and consequence of acute kidney injury: program to improve care in acute renal disease [Internet], Intensive Care Med. 37 (2) (2011) 241–248 [cited 2023 Feb 20], https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3028102/.
[40] Q. Feng, Y.H. Ai, H. Gong, L. Wu, M.L. Ai, S.Y. Deng, et al., Characterization of sepsis and sepsis-associated encephalopathy, J. Intensive Care Med. 34 (11–12) (2019) 938–945.
[41] N. Sekino, M. Selim, A. Shehadah, Sepsis-associated brain injury: underlying mechanisms and potential therapeutic strategies for acute and long-term cognitive impairments [Internet], J. Neuroinflammation 19 (2022 Apr 29) 101 [cited 2023 Feb 20], https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9051822/.
[42] T. Barichello, P. Sayana, V.V. Giridharan, A.S. Arumanayagam, B. Narendran, A. Della Giustina, et al., Long-term cognitive outcomes after sepsis: a translational systematic review [Internet], Mol. Neurobiol. 56 (1) (2019 Jan 1) 186–251, https://doi.org/10.1007/s12035-018-1048-2 [cited 2023 Feb 20].