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"CAROL DAVILA" BUCHAREST

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The Spectrum of Acute Neurological Manifestations in Sepsis and Their Prognostic Significance

PhD Dissertation Summary

Doctoral Advisor:

Professor Daniela Bartoș, MD, PhD

PhD Student:

Florin Scărlătescu, MD

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Table of Contents

Introduction.

There were several reasons behind choosing the topic for this doctoral thesis. Sepsis is one of the most commonly encountered conditions in emergency hospitals and a leading cause for admission to the intensive care unit. What has always intrigued me is the diversity seen among sepsis patients—often, patients with similar infections can have very different outcomes, with some developing complications and organ dysfunction, while others do not. The medical literature does offer some explanations, but they are often far from conclusive. Neurological dysfunction most frequently presents as coma or delirium, with altered neurological status being a key hallmark of this encephalopathy. Why do some patients show neurological dysfunction right at admission, while others with similar medical histories and lab results have no neurological issues at all? Why does neurological dysfunction occur before hospital arrival in some, but only after many days of hospitalization—or not at all—in others? The medical literature offers few answers to these questions. Moreover, most available data comes from patients already admitted to the intensive care unit. Our interest was to assess the situation at the patient's first point of contact with the hospital—on their first day of admission—regardless of whether they were eventually sent to intensive care. The research hypothesis was that certain individual characteristics—whether from medical history, previous treatments, or lab parameters identified at admission—may shape the nervous system's response to systemic infection, helping to explain the major differences in neurological symptoms seen among patients. In the following pages, I will review, one by one, the three original studies that form the foundation of this doctoral thesis.

Finally, we wish to highlight the multidisciplinary nature of our research: while the main focus of the thesis is in neurology, the broader context of the research connects with internal medicine, with applications in intensive care, hematology, and laboratory medicine.

Chapter 1. Sepsis-Associated Encephalopathy—Definition, Epidemiology, Clinical Data.

1.1 Definition and Epidemiology.

Sepsis-associated encephalopathy is a clinical syndrome resulting from sepsis-related central nervous system dysfunction, most notably marked by changes in mental status [1]. This condition is caused by the body's systemic response to infection; diagnosis requires ruling out direct microbial invasion of the central nervous system and any other simultaneous causes of encephalopathy [2]. Patients with severe sepsis account for 6.4% of emergency department visits [3] and 27% of ICU admissions [4]. Between 43.6% and 76% of these patients experience some degree of encephalopathy [5,6], making it one of the most common organ dysfunctions in sepsis. Encephalopathy may be the earliest clinical sign of sepsis [7], and any unexplained organ dysfunction should prompt suspicion for an underlying infection [8]. A combination of altered mental status, systolic blood pressure below 100mmHg, and respiratory rate above 22 breaths per minute is an effective tool to identify patients at high risk for prolonged ICU stay and in-hospital mortality due to infection [8]. Sepsis-associated encephalopathy is considered the most common encephalopathy in intensive care [9], associated with increased hospital mortality [10], even in mild cases (Glasgow score 13–14) [11,12].

1.1. Clinical Features of Sepsis-Associated Encephalopathy.

Key Points:

- Neurological symptoms can show up early, even before other organ dysfunctions or visible signs of systemic infection (early-onset encephalopathy) [1,13].
- The intensive care physician should always consider sepsis in any patient who develops changes in mood, behavior, or consciousness [7].
- Paratonic rigidity may serve as an early indicator of sepsis-associated encephalopathy, aside from altered consciousness [13].
- In most cases, sepsis-associated encephalopathy is accompanied by signs of polyneuropathy and myopathy linked to intensive care treatment [12].

- Nearly half of all survivors experience cognitive deficits one year after discharge [14], affecting their quality of life and ability to return to work [2].

Chapter 2. Sepsis-Associated Encephalopathy: Pathophysiology and Biomarkers.

1.1. Pathophysiology Essentials.

The model we suggest to help understand the pathophysiology of sepsis-associated encephalopathy is that of a fortress (the central nervous system) under siege by a powerful enemy army (in this case, the systemic inflammatory response triggered by infection). Protected behind the blood-brain barrier, the brain seems like an impenetrable stronghold. But it takes a combination of both internal and external factors for the fortress to fall: microglial activation (the soldier who has switched sides), blood-brain barrier dysfunction (the crumbling defensive wall), neuroinflammation (the fire raging inside the besieged city), disturbances in cerebral perfusion (when supply lines fail), mitochondrial dysfunction (energy resources depleted), neurotransmitter imbalance (when the peace messengers fail), and metabolic causes that can worsen encephalopathy (when the enemy gets reinforcements from its allies).

1.2. Hemostasis disorders in sepsis.

1.2.1. Coagulation in sepsis.

The relationship between coagulation and systemic inflammation is mutually reinforcing—each component stimulates and amplifies the activity of the other, and in doing so, boosts its own activity as well [15]. The involvement of the coagulation system in immune response mechanisms is supported not only by the amplification of the systemic inflammatory response but also by the multiple sources of antimicrobial peptides (kininogen, fibrinogen, coagulation factors II and X [16, 17]) and by the physical barrier role of the clot, which traps pathogens and prevents them from spreading throughout the body [15]. Thrombin is the key coagulation factor with the greatest impact on regulating the systemic inflammatory response [18].

1.2.2. Fibrinolysis in Sepsis.

Endothelial cells release tissue plasminogen activator (t-PA) and plasminogen activator inhibitor type 1 (PAI-1) into the bloodstream, which are the main regulators of fibrinolysis [15]. Initially, there is an increase (hyperfibrinolysis), which then decreases,

giving way to a persistent hypofibrinolytic state throughout the course of the illness. This has been shown in experimental studies where bacterial lipopolysaccharide (from Escherichia Coli) is injected intravenously, and the main fibrinolysis markers are tracked in serum. In these studies, t-PA and plasmin–α2-plasmin inhibitor complexes rise sharply within the first few hours after injection, peaking around three hours, indicating an early hyperfibrinolytic state. The type 1 plasminogen activator inhibitor (PAI-1) rises much more slowly, reaching its highest plasma concentration at five hours post-injection, which signals the onset of the hypofibrinolytic pattern [19]. Even though neutrophil elastase—a proteolytic enzyme that can cleave fibrin bridges and boost initial hyperfibrinolysis [15,19]—increases in serum, it cannot counteract the marked inhibition of fibrinolysis from the rise in PAI-1 [20]. In routine clinical practice, fibrinolysis inhibition is rarely diagnosed, mainly because most hospitals (outside of research labs) lack tests to measure fibrinolysis [15]. Some tests that assess the overall fibrinolysis process include: plasma clot lysis time, euglobulin clot lysis time (using the euglobulin fraction of plasma, which is low in platelets), viscoelastic testing (thromboelastography, rotational thromboelastometry—both with whole blood), and rheometric testing (also using whole blood).

1.2.3. Platelets in Sepsis.

Thrombocytopenia is considered a negative prognostic factor in sepsis; its incidence varies widely, ranging from 8% to 67% upon admission to intensive care for sepsis, with these variations largely due to differences in definitions and patient populations across studies [21]. Thrombocytopenia is not linked to a significantly increased risk of bleeding in patients with sepsis, but it is associated with poorer outcomes and higher mortality rates [21]. In cases of sepsis, an increase in platelet count has been observed alongside the early onset of sepsis-associated encephalopathy. In a retrospective observational study published in 2024, we demonstrated a link between the presence of early sepsis-associated encephalopathy and elevated platelet count, faster clot propagation phase, and greater clot firmness and elasticity (both closely tied to platelet numbers) [22].

1.2.4. Stages of Sepsis-Induced Coagulopathy.

In a further analysis of two clinical trials involving patients with sepsis (HYPRESS, which evaluated the benefits of hydrocortisone in preventing septic shock, and SISPCT, which investigated the effects of sodium selenite administration and therapy guidance based on procalcitonin levels on mortality in severe sepsis and septic shock [23,24]), the prevalence of sepsis-induced coagulopathy was 22% and 24%, respectively. In both studies, the presence of sepsis-induced coagulopathy was linked to higher mortality rates [25]. Three stages of sepsis-induced coagulopathy have been identified: masked disseminated intravascular coagulation, thrombotic, and overt [15].

1.3. Biomarkers for sepsis-associated encephalopathy.

Identifying biomarkers linked to sepsis-associated encephalopathy would provide crucial clinical tools to help flag septic patients at risk of developing brain dysfunction, or those already experiencing encephalopathy. These biomarkers could also offer guidance for further interventions aimed at reducing brain injury. The literature describes three main categories of biomarkers: electrical, molecular (the most frequently found, from blood or cerebrospinal fluid), and imaging biomarkers.

Chapter 3. Working Hypotheses and General Objectives of the Study.

The goal of this work is to provide a detailed overview of neurological complications in patients with sepsis, covering clinical presentations, severity, and prognostic value. Special attention will be given to identifying molecular and imaging biomarkers associated with the onset and/or severity of sepsis-related encephalopathy. **The central hypothesis is that individual differences (including phenotypic traits, biological factors, and comorbidities) influence how the central nervous system responds to sepsis, which may explain variations in the presence, severity, and progression of encephalopathy among patients. By pinpointing these factors that shape the brain's response to sepsis, we aim to develop clinical tools (biomarkers) with prognostic value, which will be useful in assessing septic patients going forward.**

Chapter 4. The Range of Acute Neurological Manifestations in Sepsis and Their Prognostic Significance.

4.1 Study Objectives were:

1. Description of the types of encephalopathy observed in patients with sepsis at hospital admission, along with analysis of the relationships between encephalopathy type, severity of symptoms, and short-term outcomes (such as survival rate, length of hospital stay, and duration of intensive care unit admission).
2. Identification of molecular or imaging biomarkers linked to the onset of encephalopathy. 6
3. Clarifying the role of various chronic or acute comorbidities in the development of encephalopathy.

Materials and Methods: This is a single-center, prospective observational (non-interventional) study conducted at the Bucharest Clinical Emergency Hospital starting in January 2020. The hospital's Ethics Committee approved the study; given its non-interventional nature and use solely of clinical and laboratory data gathered during routine patient care, no additional informed consent was required, though written consent for the use of medical data was documented in the medical records, in line with the institution's internal policies.

4.2.1. Inclusion and exclusion criteria.

Inclusion criteria: Patients with medically induced sepsis, with or without encephalopathy, and with or without the need for intensive care admission. Enrollment occurred as close to the time of hospital admission as possible, and participants were over 18 years old. Exclusion criteria: Patients with surgically induced sepsis, ongoing pregnancy, refusal to participate, age under 18, or uncorrected acute respiratory failure. All patients received a standard evaluation, and an examination sheet was completed with all study variables. The type of encephalopathy identified at admission (pure septic, probable septic, likely multifactorial, or definitely multifactorial) was assessed based on the clinical presentation and possible confounding factors such as pre-existing neurocognitive disorders or other simultaneous causes of encephalopathy (hepatic, hypo- or hyperglycemic, hypo- or hypernatremic, uremic).

4.3. Results.

4.3. Demographic Data and Study Group Description.

A total of 233 patients were enrolled in the study, including 102 men (43.78%) and 131 women (56.22%). Forty-six patients (representing 19.74%) did not show any encephalopathy at admission: 180 patients (77.25%) showed varying degrees of encephalopathy. When looking at the distribution by gender, there were no significant differences between males and females regarding the prevalence of encephalopathy at the time of admission. Nearly half of the patients in the study (48.93%) had at least one neuropsychiatric comorbidity. Additionally, 14.59% of the patients had two neuropsychiatric comorbidities, and 2.16% had three neuropsychiatric comorbidities. The purely septic form of encephalopathy was found in 55 patients (23.60%), while a multifactorial form (accompanied by significant metabolic imbalances consistent with the severity of encephalopathy) was found in 53 patients (22.75%). Twelve patients (5.15%) with an ambiguous clinical picture could not be classified as having or not having encephalopathy. The most common clinical sign of encephalopathy was coma. Of all the patients with encephalopathy, more than half (56.11%) were comatose at the time of admission.

4.3.1. What information can we get from routine biological samples collected at admission?

The following variables from the complete blood count are statistically significantly associated with the occurrence of encephalopathy at admission:

- Red cell distribution width ($p=0.026$).
- Platelet distribution width measured 24 hours after hospital admission ($p=0.031$).
- Mean platelet volume ($p=0.034$).

Among the standard biochemical tests collected at admission, the following showed a statistically significant correlation with the presence of encephalopathy at admission: serum creatinine level ($p=0.001$), blood urea ($p=0.001$), and serum sodium ($p=0.030$). There were also statistically significant associations found between pure septic encephalopathy and:

- Serum creatinine level ($p<0.001$)
- Serum urea level ($p<0.001$).

4.3.3 Correlations with demographic data and hospital admission details. Mortality Analysis.

There is no statistically significant correlation between age and the presence of any type of encephalopathy at admission. Furthermore, when specifically examining the subgroup of patients with pure encephalopathy, broken down by age groups, no statistically significant associations were observed between age groups and the presence of neurological impairment. However, having encephalopathy at the time of hospital admission does impact the length of hospitalization. Thus, any type of neurological dysfunction identified at hospitalization leads to a statistically significant increase in ICU stay, while cases of encephalopathy directly related to sepsis do extend the hospital stay but do not significantly affect the length of time spent in intensive care. Mortality analysis showed that both any type of neurological dysfunction and pure septic encephalopathy are statistically linked to in-hospital death.

4.3.4. Identifying the infectious agent and the primary site of infection.

The most common sources of primary infections leading to sepsis are found in the urinary tract, lungs, and skin. In many cases, patients are admitted with not just one, but two or even three infection sites, resulting in sepsis being categorized as having multiple origins. There are also instances in which the source of sepsis remains unidentified. Statistical analysis regarding the primary site of infection yielded interesting findings: the location of the initial infection is significantly associated with both the development of any type of neurological dysfunction at admission and with early septic encephalopathy (purely septic) detected upon hospital entry. Bacteriological tests on the study group revealed that one or more pathogens were present in 146 patients, accounting for about 63% of the group.

Further analysis showed that a higher number of identified pathogens is significantly associated with both any form of neurological dysfunction ($p=0.001$) and pure septic encephalopathy at admission ($p=0.038$).

4.3.5. What insights can we gain from brain imaging via CT scan performed at hospital admission?

Less than half of the patients in the study group underwent brain CT scanning upon admission. These scans were not done routinely (which would have compromised the non-invasive nature of the study, given the risks of exposure to ionizing radiation), but were carried out solely based on the attending physician's clinical judgment—for differential diagnosis of neurological status changes at admission, and, in a smaller number of cases, due to suspicion of acute cerebral ischemia.

At this stage, our research questions focused on whether there might be any links between chronic vascular or degenerative disease (as seen on CT imaging) and the development of encephalopathy in sepsis. All the questions above received negative answers, except for a statistically significant connection between frontal lobe abiotrophy and the presence of pure septic encephalopathy at admission. This, similar to the link found with a history of dementia, points to a shared underlying factor between these conditions: neuroinflammation.

4.4 Discussion, Partial Conclusions, Study Limitations.

The purpose of this study was to provide an overview of early neurological impairment in sepsis. Unlike most published data—which typically includes septic patients meeting intensive care admission criteria—our study enrolled patients on their first day of hospitalization, regardless of case severity or ICU admission, and followed them throughout their stay. A remarkably high percentage of patients (over 77%) showed some level of encephalopathy upon hospital admission. This figure is notable, as it exceeds existing literature, which generally focuses on advanced sepsis cases with multiple organ dysfunctions requiring intensive care. One likely explanation for this high rate of encephalopathy at admission in our study group is delayed presentation and a high prevalence of associated comorbidities. Most patients in our group were elderly (with only 16% under the age of 60), often had a history of neurological or psychiatric disorders, and at least two additional non-neuropsychiatric comorbidities. From the outset, our focus was on the early form of encephalopathy strictly related to the host's response to infection (pure septic, early onset). The prevalence of encephalopathy directly linked to the host's response—rather than other metabolic or biological imbalances—was over 40% in our group (including both pure and probable septic cases), with more than half of these cases showing no other confounding causes. We believe that targeted analysis of this patient subgroup should be a future research priority. The presence of any type of encephalopathy at admission extends the length of time spent in intensive care, unlike pure septic encephalopathy. This is likely because other contributing organ dysfunctions require more aggressive treatment, which also affects neurological function. Interestingly, there's a statistically significant but inverse relationship between pure septic encephalopathy and the length of hospitalization: patients admitted with pure septic encephalopathy actually tend to have shorter hospital stays. We believe this finding isn't directly related to the encephalopathy itself but rather in the absence of other major organ dysfunctions that could contribute to neurological issues. Any type of neurological impairment at admission increases the risk of mortality. The patients' medical history also provides some intriguing insights. For instance, a history of dementia is significantly associated with early, pure septic encephalopathy, but not with neurological dysfunction of any kind at admission. The common thread between these two associated conditions is inflammation, specifically neuroinflammation within the brain, which plays a role in both neurodegenerative diseases and sepsis-related encephalopathy. Among general comorbidities, the absence of a history of chronic kidney failure is

statistically linked to early, pure septic encephalopathy, supporting the author's careful selection of encephalopathy case. Some fascinating findings came from the analysis of biological samples taken at admission. The red blood cell distribution width showed a significant correlation with the presence of neurological dysfunction at admission; the underlying factor here is systemic inflammation tied to substantial oxidative stress, which shortens the average lifespan of red blood cells and explains their phenotypic differences. Likewise, platelet distribution width measured 24 hours after admission (but not at admission itself) was correlated with the presence of encephalopathy at admission, reflecting the same underlying process but highlighting its dynamic evolution. There was a statistically significant association between two parameters with partially shared pathogenic roots, where encephalopathy preceded changes in the other parameter by about 24 hours. The central nervous system's heightened sensitivity to inflammation explains why, at times, encephalopathy is the only clinical sign of sepsis—even when there's no obvious focal infection. Another platelet-related marker, mean platelet volume, was also significantly associated with encephalopathy at admission, with changes interpreted within the same systemic inflammatory context. These same parameters either correlated or nearly correlated (just missing statistical significance) with the pure septic form of encephalopathy, underscoring the role of systemic inflammation in its development. Among biochemical markers, those indicating nitrogen retention were significantly associated with any neurological dysfunction at admission (highlighting the importance of uremic encephalopathy in multifactorial cases) and were inversely, and significantly, associated with the pure septic form of encephalopathy. Finally, coagulopathy detected through conventional tests (spontaneously elevated INR) was linked to any type of neurological dysfunction, but not to the pure septic form of encephalopathy at admission, with the former association largely due to cases of multifactorial encephalopathy. The topic of sepsis-related coagulopathy will be discussed as a priority in the second clinical study included in this doctoral thesis (chapter 5). Systemic inflammation biomarkers would have been extremely helpful, but they were missing in most cases at admission, due to technical or financial constraints related to hospitalization at that time. We consider this to be one of the main limitations of this study.

We thought it would be a valuable research question to explore whether the infection site or the specific infectious agent identified plays a role in the onset of neurological dysfunction. Indeed, the location of the primary infection shows a statistically significant correlation with the development of neurological dysfunction; the most common primary infection sites are urinary and pulmonary, organs innervated by the vagus nerve (allowing direct intraneural transmission of local inflammatory signals). The microbial load in each case (measured here by the number of identified pathogens) is also significantly correlated both with any kind of neurological dysfunction and with early, pure septic encephalopathy.

Another noteworthy finding emerged from the brain imaging analysis of the patients in the study group. Specifically, early-onset pure septic encephalopathy observed at admission showed a significant statistical association with the severity of frontal lobe atrophy (measured using the GCA scale), but not with the presence of older frontal infarcts, which were also documented through imaging. This once again highlights the key role of neuroinflammation as a common thread linking neurodegenerative disorders (such as dementia and cerebral atrophy markers) and sepsis-related encephalopathy. Damage to other brain regions—especially the temporal lobes—did not reach statistical significance in terms of association with early pure encephalopathy during the course of sepsis.

Therefore, if we were to outline the profile of the ideal candidate for early-onset pure septic encephalopathy, it would be a patient with a history of dementia and significant temporal lobe atrophy, a general medical background without neuropsychiatric conditions, who most likely develops a urinary or respiratory infection—whether fungal or polymicrobial—and in whom the first subtle biological changes are detected in the blood count.

4.4.1. Study Limitations.

It would have been helpful to have additional biological data to better measure systemic inflammation, but unfortunately, these were not available at the hospital when patients were enrolled in the study. The bacteriological analysis uncovered many cases where identifying the infectious agent was unsuccessful, either because it was impossible to collect targeted biological samples or for other reasons. Of course, brain imaging by MRI would have provided superior information, but this limitation was intentionally accepted by the author in order to use more accessible diagnostic tools to carry out and interpret. Moreover,

performing a brain MRI would have been considerably more challenging, especially for patients who are hemodynamically unstable, require special ventilation positions, or need sedation for optimal imaging. A major source of confusion also relates to admission to the intensive care unit, which can sometimes depend on limited bed availability or additional admission criteria, such as grouping patients with similar infectious profiles).

Chapter 5. Correlations between hemostatic parameters and early onset of sepsis-associated encephalopathy.

5.1. Introduction.

This second study included in this doctoral thesis builds upon the previous one, whose results were thoroughly detailed in Chapter 4. This time, we will focus specifically on the primary objective of the study, without repeating the descriptive analysis of the study group, as it closely resembles the group from the first study. The study was published in The Journal of Critical Care Medicine in 2024 [22].

5.2. Study Objectives.

This study was centered around two primary objectives: a comprehensive assessment of coagulation in patients with early-stage sepsis-associated encephalopathy, and a comparison of hemostatic parameters between septic patients with and without encephalopathy within the first 24 hours following sepsis diagnosis.

5.3 Materials and Methods.

This observational retrospective study involved patients diagnosed with sepsis within the first 24 hours, focusing specifically on cases with early-onset (purely septic) encephalopathy). Exclusion criteria covered patients with coagulopathies due to medication or associated comorbidities, such as Child-Pugh class B and C liver cirrhosis, moderate to severe chronic kidney disease (KDIGO CKD Work Group stages 3, 4, 5), those receiving anticoagulant or antiplatelet therapy, or those who had been given procoagulant treatment —this included blood products—during the week prior to study enrollment. Data was collected from two clinical centers, with both receiving approval from their respective Ethics Committees. Blood tests were performed on all patients within the first 24 hours of study enrollment. Due to logistical considerations, the testing panels varied among patients: 118 patients had access to a complete blood count and additional hemostasis tests, while 162 patients had only a complete blood count within the first 24 hours, and in some cases standard hemostatic parameters. The parameters assessed included: routine coagulation tests, plasma levels of pro- and anticoagulant factors, plasma D-dimer concentration, and rotational thromboelastometry using a ROTEM Delta system with reagents and standard materials provided by the manufacturer.

5.4. Results.

The study included 280 patients (52.1% men) with a mean age (SD) of 69.64 (15.27) years. The prevalence of sepsis-associated encephalopathy in the group was 65.7%.

There was a statistically significant correlation between platelet count and the occurrence of sepsis-associated encephalopathy. Comparing the two subgroups (with and without encephalopathy), the results can be summarized as follows: both groups showed slightly elevated median prothrombin times (above the lab's normal range) and lower average plasma levels of both procoagulant and anticoagulant factors (compared to the lower limit of normal). The two subgroups did not differ in the initiation of coagulation, but patients with encephalopathy showed a faster propagation phase, as evidenced by a quicker clot formation speed and shorter clot formation time on ROTEM. Clot firmness and elasticity—as well as the platelet contribution (difference in elasticity between EXTEM and FIBTEM)—were higher in encephalopathic patients compared to those with normal neurological exams. There was no difference between the groups regarding clot lysis. Plasma fibrinogen levels were also similar between the groups. Despite this, encephalopathic patients had greater clot resistance on FIBTEM than those without encephalopathy. The significance of the increased clot resistance observed in encephalopathic patients was further assessed by including plasma fibrinogen levels and platelet contribution in a multivariable logistic regression model, and the results confirmed that platelet contribution is a significant predictor of encephalopathy after adjusting for serum fibrinogen levels.

5.5. Discussion.

This study demonstrated a statistically significant link between early development of sepsis-associated encephalopathy and platelet count, faster coagulation propagation, and increased clot strength driven by platelet activity. These findings are especially noteworthy because changes in platelet count and coagulation during the early stages of sepsis (as opposed to advanced stages) are generally subtle or even appear normal. Another important takeaway is the critical role of using ROTEM for thorough assessment of septic patients right from the onset of illness.

Chapter 6: Clinical, Imaging, and Laboratory Correlations in Adult Patients Presenting with Sepsis to the Emergency Department: Results from a Single-Center Retrospective Observational Study.

This chapter summarizes early correlations between sepsis-associated encephalopathy at hospital admission and various biological or imaging parameters, with a focus on the differences found between patients with multifactorial neurological dysfunction and those with pure sepsis-related encephalopathy. The findings of this study have been published in the Juntendo Clinical Journal [26].

6.1. Study Objectives: To identify and review clinical, imaging, and biological correlations in patients with early-stage sepsis-associated encephalopathy, and to highlight the differences between those with pure septic encephalopathy and those with multifactorial encephalopathy.

Key Questions:

1. What are the differences in the clinical profile between patients with pure septic encephalopathy and those with multifactorial encephalopathy?
2. What are the biological and imaging distinctions between these two patient groups?

6.2. **Materials and Methods.**

A total of 226 patients diagnosed with sepsis according to Sepsis Criteria-3[8] were included in this study, which received ethical approval from the institution's specialty committee (2257/22.01.2024). The inclusion criteria mirrored those described in Chapter 4.

6.3. Results.

180 patients (80% of the study group) showed some degree of encephalopathy upon hospital admission, with approximately a quarter of them (56 patients, 24.8%) presenting with the pure form of encephalopathy [26].

6.4. **Demographic data**:

The average age in the subgroups with and without encephalopathy was similar (72.54 and 73.26 years, respectively). Patients with the pure form of encephalopathy tended to be slightly younger (average age 70.5 vs. 73.3 years), but this difference was minor and not statistically significant. The gender distribution was almost the same between those with pure septic encephalopathy and those with multifactorial encephalopathy (men accounted for 42.2% and 44.6% in the two groups). Patients with and without any type of neurological

dysfunction at admission did not show significant statistical differences in terms of associated chronic comorbidities. The situation remained relatively consistent when comparing patients with and without pure septic encephalopathy—except for chronic kidney failure (which is more common in the group without pure encephalopathy) and liver cirrhosis (found only in the group without pure encephalopathy)—support the accuracy of classifying cases as pure septic encephalopathy. Additionally, the presence of neurological dysfunction in patients with chronic kidney failure and liver cirrhosis points to a multifactorial type of encephalopathy [26].

Organ Dysfunction, Lab Findings, Prognosis.Patients who present with any form of neurological dysfunction at admission have a higher red blood cell distribution width and platelet volume compared to those without neurological issues, indicating distinct hematologic activation between the groups. These patients also show elevated levels of nitrogenous waste products, sodium, and INR, suggesting broader organ dysfunction and requiring a longer stay in intensive care (although the total length of hospitalization isn't significantly different from patients without neurological dysfunction [26]). In patients with sepsis-associated pure encephalopathy, hematologic parameters do not differ significantly from the group without pure encephalopathy, though the former seem to have better renal function (lower urea and serum creatinine) and shorter hospital stays (with no significant difference in intensive care admission [26]). In the multivariate model restricted to hematologic and laboratory parameters, none reached statistical significance regarding independent association with neurological dysfunction at admission. In contrast, in the model for sepsis-associated pure encephalopathy, red cell distribution width and serum creatinine were identified as independent predictors. For every 1% increase in red cell distribution width, the odds of developing sepsis-associated pure encephalopathy rise by 20% after adjusting for other lab variables in the model. Each 1 mg/dl increase in serum creatinine reduces the chance of being classified as having sepsis-associated pure encephalopathy by 23% [26].

6.3.3. Brain Imaging.

The data concerning brain imaging procedures, image analysis, and the various parameters used to assess vascular or neurodegenerative pathological load are similar to those outlined in Chapter 4, Subchapter 4.3.6, and will not be repeated here to avoid duplicating information already published in another section of the thesis. To summarize the analysis of these data: both microvascular and macrovascular cerebrovascular pathological loads appear similar across the different study groups (with and without global neurological dysfunction, with and without sepsis-associated pure encephalopathy), except for the frontal lobe atrophy score (frontal GCA), which is statistically significantly associated with sepsis-associated pure encephalopathy [26].

6.4. Discussions, Conclusions.

Septic patients who have neurological impairment when admitted have a lower survival rate compared to those without such issues; this holds true both for any kind of neurological dysfunction at admission (26% vs. 67.3%) and for the subgroup with sepsis-associated encephalopathy (19.6% vs. 39.4%), in line with previously published literature [27]. The significance of this data lies in expanding the current body of evidence by showing that neurological dysfunction identified at the patient's first contact with the hospital, in the emergency department—before any potential sedation, fluid resuscitation, or other confounding factors from intensive care—leads to a worse prognosis, regardless of whether ICU admission is later required. This early assessment perspective is particularly important because most earlier studies only evaluated neurological status after ICU admission, when many confounding factors could have already affected the neurological picture [26].

Of all the biological parameters studied, red cell distribution width is the only independent predictor associated with pure septic encephalopathy in the multimodal analysis model, a finding that aligns with current scientific literature. For example, a 2020 meta-analysis by Zhang established a statistically significant correlation between red cell distribution width and mortality in sepsis [28], while Singh and colleagues demonstrated that red cell distribution width outperforms serum lactate in predicting mortality during sepsis [29]. The link between red cell distribution width and sepsis-associated encephalopathy is therefore clear, as systemic inflammation driven by sepsis increases oxidative stress, which has a major impact on red blood cell biology. Furthermore, an increased red cell distribution width suggests impaired erythrocyte deformability and microvascular dysfunction. Given how crucial a healthy microcirculation is for optimal brain function, it can be suggested that changes in red blood

cell rheology may contribute to localized cerebral ischemia and elevate metabolic stress in affected brain regions [26]. The inverse relationship between serum creatinine levels and the presence of pure sepsis-associated encephalopathy is consistent with the study's criteria for identifying and including patients (as detailed in Chapter 4 of this thesis).

Current literature suggests that preexisting vulnerabilities in the brain, such as degenerative or vascular lesions, increase the risk of developing delirium during sepsis [26]. Pendlebury and colleagues demonstrated that changes in cerebral white matter and cortical atrophy, as shown in imaging studies up to five years prior to the current hospital admission for either a completed or transient ischemic stroke, patients were found to experience delirium during their hospital stay [30].

The frontal lobe appears to serve as a key vulnerability point in the development of sepsis-induced neurological dysfunction, as shown by functional brain MRI studies conducted on sepsis survivors [31]. Nakae and colleagues reported ongoing loss of brain volume during intensive care treatment for sepsis, with an average reduction of 3.7% in brain volume over 31 days [32]. The findings of this current study, which examined the presence of cortical atrophy at hospital admission, complement previous reports documenting brain volume loss during sepsis hospitalization: patients who already have frontal lobe atrophy seem more susceptible to developing sepsis-associated encephalopathy, and sepsis itself further accelerates brain tissue loss [26].

This study's approach, relying on straightforward data collected in the emergency department at the patient's first point of contact with the hospital, marks a paradigm shift—from identifying septic encephalopathic patients in the ICU to recognizing neurological dysfunction right at the start. The time spent in the emergency department becomes the crucial window for early detection and rapid intervention, before sedation, mechanical ventilation, or other intensive care factors can alter the neurological picture. Explicitly distinguishing between pure sepsis-associated encephalopathy and other forms of encephalopathy introduces a conceptual refinement rarely addressed in the literature, with significant implications for both diagnosis and patient management [33].

6.5. Study Limitations.

The main limitations of this study stem from its retrospective, single-center, observational design, which may restrict the generalizability of the findings. The number of patients with available brain imaging was fairly low (92 patients, of whom 84 had neurological dysfunction), reducing the statistical power to detect differences between groups. The diagnosis of pure sepsis-associated encephalopathy is primarily clinical and naturally involves a degree

of subjectivity. Finally, survival could only be assessed at hospital discharge, leaving long-term survival and associated neurocognitive outcomes unaddressed [26].

Chapter 7. Conclusions and Personal Contributions.

The theoretical model introduced in the general section of this paper for understanding the pathophysiology of sepsis-associated encephalopathy highlights the multiple layers of defense the central nervous system mounts against systemic infectious threats, and is at least partially supported within the limits of our findings. In the section on personal contributions I identified several conditions associated with brain distress in sepsis. I was able to meet, to a significant extent, the research project's objectives related to describing the range of neurological symptoms in the acute phase of sepsis (along with identifying their associations with clinical and paraclinical elements that could serve as biomarkers for sepsis-associated encephalopathy), as well as establishing their prognostic correlations. However, due to objective limitations in patient follow-up, further work is needed to clarify the potential contribution of sepsis to long-term neurocognitive and cerebrovascular impairment. Some challenges stemmed from limited technical and economic resources within the hospital—for example, the absence of systemic inflammation markers at admission for some patients—making research development more difficult and steering it toward alternative directions. Encephalopathy was observed in over 77% of septic patients enrolled in the study presented in Chapter 4 (and for a third of these patients, sepsis was the only identifiable cause of encephalopathy), a noticeably higher percentage, especially considering that patients were enrolled upon hospital admission, unlike most literature data where patients are usually admitted to intensive care. We do not have a definitive explanation for this, but a later presentation to the emergency room could be among the possible factors, along with the overall disease burden, as at least half of the patients had a history of neurological illness (most commonly dementia and vascular sequelae), and two-thirds had at least two prior chronic medical conditions, most frequently cardiovascular disease, diabetes, or chronic kidney disease. The most common neurological symptom at admission was coma, followed by delirium and confusion. What stands out, compared to the literature, is the extremely low number of cases with motor manifestations of sepsis-associated encephalopathy. Some possible explanations include the early timing of the neurological exam or the masking of subtle motor symptoms by the more dominant general clinical picture at admission. The presence of any neurological dysfunction at hospital admission extended the length of stay in intensive care, while cases of encephalopathy strictly related to sepsis did not affect ICU stay

but were linked to longer hospitalizations overall. The patient's medical history is relevant for the development of sepsis-associated encephalopathy: any type of dementia is tied to the early onset of pure sepsis-related encephalopathy, likely due to the shared underlying feature of neuroinflammation. It is no coincidence that brain imaging analysis in septic patients confirmed a statistically significant association between frontal lobe atrophy and early septic encephalopathy.

The history of frontal lobe ischemia does not seem to carry the same weight, once again highlighting the role of neuroinflammation—which diffusely impacts the brain and leads to an overall reduction in its volume—in the development of sepsis-associated encephalopathy in patients with chronic neurodegenerative conditions. The analysis of biological parameters tested at admission offers some intriguing insights. Simple measures like red cell distribution width, platelet volume, and platelet distribution width measured 24 hours after admission show a correlation with neurological dysfunction due to sepsis present at hospital entry; inflammation is a key factor in this link. Spontaneous coagulopathy at admission (reflected by elevated INR) is, once more, connected with early neurological dysfunction in sepsis. These very findings guided us toward conducting the second study included in the general section of this thesis, focused on hemostatic parameters in sepsis.

The study confirmed the hyperactive nature of coagulation in sepsis and its association with the early onset of encephalopathy, and also reinforced the connection between platelets and the development of encephalopathy. Further, interesting data emerged from the analysis related to the primary infection that triggers sepsis. Microbial load, represented by the number of pathogenic organisms identified in the patient's biological samples, is linked to both general neurological dysfunction and sepsis-specific encephalopathy. Fungal sepsis is associated with the early onset of pure septic encephalopathy. Among bacteria, Klebsiella pneumoniae points to the same conclusion. The long-term prognostic value of sepsis-associated encephalopathy remains unclear beyond hospital discharge. A future hypothesis to explore is that sepsis may serve as a trigger for neurodegenerative diseases, based on the premise that sepsis initiates the neuroinflammatory process and sustains central nervous system inflammation, leading to neurocognitive decline, with or without imaging evidence. We see this as an excellent direction for further research in the field. In Chapter 5 of this thesis, we demonstrated a statistically significant correlation between coagulopathy and early-onset sepsis-associated encephalopathy (documented at admission) and established the usefulness of ROTEM for thorough coagulation assessment in septic patients, particularly since early-phase platelet and coagulation changes are often subtle. In this thesis, we also introduced and widely applied the concept of pure-form

sepsis-associated encephalopathy, defined as the absence of any other factors that might alter neurological status at the time of examination. We demonstrated a statistically significant correlation between this encephalopathy subtype and increases in distribution width of red blood cell distribution, highlighting the role of systemic inflammation as a driving factor for both conditions (see Chapter 6).

In conclusion, we would like to emphasize our own contributions to research in this field. The proposed theoretical model for understanding the pathophysiology of sepsis-associated encephalopathy (the "besieged fortress" model) is an original concept, and we believe it serves as an especially valuable learning tool (see Chapter 2, Section 2.1). Another unique contribution is the study of sepsis-related encephalopathy in a group of patients at the time of hospital admission (outside of intensive care; see Chapter 4, Section 4.2.1). Distinguishing between the various subtypes of encephalopathy and specifically analyzing the group whose only identified cause was sepsis is yet another original addition (see Chapter 4, Section 4.2.2 and following, as well as Chapter 5, Section 5.3). The use of brain imaging by computed tomography (rather than magnetic resonance imaging, which is more complex, time-consuming, resource-intensive, and harder to perform in critically ill patients with multiple organ dysfunctions) represents a further original contribution (see Chapter 4, Section 4.3.6).

Selected references

[1]. Consales G, De Gaudio AR. Sepsis associated encephalopathy. Minerva Anestesiol. 2005 Jan-Feb;71(1-2):39-52.

[2]. Chaudhry N, Duggal AK. Sepsis Associated Encephalopathy. Adv Med. 2014;2014:762320. doi: 10.1155/2014/762320. Epub 2014 Sep 30. PMID: 26556425; PMCID: PMC4590973.

[3]. Rezende E, Silva JM Jr, Isola AM, Campos EV, Amendola CP, Almeida SL. Epidemiology of severe sepsis in the emergency department and difficulties in the initial assistance. Clinics (Sao Paulo). 2008 Aug;63(4):457-64.

[4]. Silva E, Almeida PM, Sogayar ACB, Mohovic T, Oliveira SCL, Janiszewski M, et al. Brazilian Sepsis Epidemiological Study (BASES study) Crit Care. 2004;8:R251–R260. doi: 10.1186/cc2892.

[5]. Chen, J., Shi, X., Diao, M. et al. A retrospective study of sepsis-associated encephalopathy: epidemiology, clinical features and adverse outcomes. BMC Emerg Med 20, 77 (2020).

[6]. Schramm P, Klein KU, Falkenberg L, Berres M, Closhen D, Werhahn KJ, David M, Werner C, Engelhard K. Impaired cerebrovascular autoregulation in patients with severe sepsis and sepsis-associated delirium. Crit Care. 2012 Oct 4;16(5):R181.

[7]. Mazeraud A, Righy C, Bouchereau E, Benghanem S, Bozza FA, Sharshar T. Septic-Associated Encephalopathy: a Comprehensive Review. Neurotherapeutics. 2020 Apr;17(2):392-403.

[8]. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):801–810.

[9]. Bleck TP, Smith MC, Pierre-Louis SJ, Jares JJ, Murray J, Hansen CA. Neurologic complications of critical medical illnesses. Crit Care Med. 1993;21:98–103.

[10]. Sonneville R, de Montmollin E, Poujade J, Garrouste-Orgeas M, Souweine B, Darmon M, Mariotte E, Argaud L, Barbier F, Goldgran-Toledano D, Marcotte G, Dumenil AS, Jamali S, Lacave G, Ruckly S, Mourvillier B, Timsit JF. Potentially modifiable factors contributing to sepsis-associated encephalopathy. Intensive Care Med. 2017 Aug;43(8):1075-1084.

[11]. Sonneville R, Benghanem S, Jeantin L, de Montmollin E, Doman M, Gaudemer A, Thy M, Timsit JF. The spectrum of sepsis-associated encephalopathy: a clinical perspective. Crit Care. 2023 Oct 5;27(1):386.

[12]. Eidelman LA, Putterman D, Putterman C, Sprung CL. The spectrum of septic encephalopathy. Definitions, etiologies, and mortalities. JAMA. 1996 Feb 14;275(6):470-3.

[13]. Gofton, T., Young, G. Sepsis-associated encephalopathy. Nat Rev Neurol 8, 557–566 (2012).

[14]. Hopkins R. O., Weaver L. K., Chan K. J., Orme J. F., Jr. Quality of life, emotional, and cognitive function following acute respiratory distress syndrome. Journal of the International Neuropsychological Society. 2004;10(7):1005–1017.

[15]. Scarlatescu, F.; Scarlatescu, E.; Thachil, J.; Tomescu, D.R.; Bartos, D. The Fibrinolytic System in Bacterial Sepsis: A Comprehensive Review of Current Assessment Methods. J. Clin. Med. 2025, 14, 6055.

[16]. Nickel KF, Renné T. Crosstalk of the plasma contact system with bacteria. Thromb Res. 2012 Oct;130 Suppl 1:S78-83.

[17]. van der Poll T, Herwald H. The coagulation system and its function in early immune defense. Thromb Haemost. 2014 Oct;112(4):640-8.

[18]. Ma L, Dorling A. The roles of thrombin and protease-activated receptors in inflammation. Semin Immunopathol. 2012 Jan;34(1):63-72.

[19]. Suffredini AF, Harpel PC, Parrillo JE. Promotion and subsequent inhibition of plasminogen activation after administration of intravenous endotoxin to normal subjects. N Engl J Med. 1989 May 4;320(18):1165-72.

[20]. Gando S, Hayakawa M, Sawamura A, Hoshino H, Oshiro A, Kubota N, Jesmin S. The activation of neutrophil elastase-mediated fibrinolysis is not sufficient to overcome the fibrinolytic shutdown of disseminated intravascular coagulation associated with systemic inflammation. Thromb Res. 2007;121(1):67-73.

[21]. Hui P, Cook DJ, Lim W, Fraser GA, Arnold DM. The frequency and clinical significance of thrombocytopenia complicating critical illness: a systematic review. Chest. 2011 Feb;139(2):271-278.

[22]. Scarlatescu F, Scarlatescu E, Tomescu DR, Bartos D. The Correlation of Hemostatic Parameters with the Development of Early Sepsis-Associated Encephalopathy. A Retrospective Observational Study. J Crit Care Med (Targu Mures). 2024 Oct 31;10(4):329-336.

[23]. Keh D, Trips E, Marx G, et al. Effect of Hydrocortisone on Development of Shock Among Patients With Severe Sepsis: The HYPRESS Randomized Clinical Trial. JAMA. 2016;316(17):1775–1785.

[24]. Bloos F, Trips E, Nierhaus A, Briegel J, Heyland DK, Jaschinski U, Moerer O, Weyland A, Marx G, Gründling M, Kluge S, Kaufmann I, Ott K, Quintel M, Jelschen F, Meybohm P, Rademacher S, Meier-Hellmann A, Utzolino S, Kaisers UX, Putensen C, Elke G, Ragaller M, Gerlach H, Ludewig K, Kiehntopf M, Bogatsch H, Engel C, Brunkhorst FM, Loeffler M, Reinhart K; for SepNet Critical Care Trials Group. Effect of Sodium Selenite Administration and Procalcitonin-Guided Therapy on Mortality in Patients With Severe Sepsis or Septic Shock: A Randomized Clinical Trial. JAMA Intern Med. 2016 Sep 1;176(9):1266-76.

[25]. Schmoch T, Möhnle P, Weigand MA, Briegel J, Bauer M, Bloos F, Meybohm P, Keh D, Löffler M, Elke G, Brenner T, Bogatsch H; SepNet–Critical Care Trials Group. The prevalence of sepsis-induced coagulopathy in patients with sepsis - a secondary analysis of two German multicenter randomized controlled trials. Ann Intensive Care. 2023 Jan 12;13(1):3.

[26]. Scarlatescu F, Scarlatescu E, Bartos D, Early clinical, laboratory, and imaging correlates of neurological dysfunction in adults presenting to the emergency department with sepsis: a single-center retrospective study, Juntendo Medical Journal, 2026.

[27]. Sprung CL, Peduzzi PN, Shatney CH, et al. Impact of encephalopathy on mortality in the sepsis syndrome. The Veterans Administration Systemic Sepsis Cooperative Study

Group. Critical care medicine 1990;18(8):801-6.

[28]. Zhang L, Yu C-h, Guo K-p, Huang C-z, Mo L-y. Prognostic role of red blood cell distribution width in patients with sepsis: a systematic review and meta-analysis. BMC Immunology 2020;21(1):40.

[29]. Singh S, Diwakar N, Jha R, Vatsa P, Ahmad A. Assessing the Prognostic Accuracy of Red Cell Distribution Width for Predicting Mortality in Sepsis Patients: A Comparative Study With Serum Lactate and the Quick Sequential Organ Failure Assessment (qSOFA) Score. Cureus 2025;17(3):e80056.

[30]. Pendlebury ST, Thomson RJ, Welch SJV, Kuker W, Rothwell PM, Study ftOV. Utility of white matter disease and atrophy on routinely acquired brain imaging for prediction of long-term delirium risk: population-based cohort study. Age and Ageing 2021;51(1).

[31]. Li Y, Chen JQ, Wang H, Yang JJ, Ji MH. Frontal, temporal, cerebellar changes link to sepsis survivors' cognitive issues: A resting state functional magnetic resonance imaging study. World journal of psychiatry 2025;15(10):108861.

[32]. Nakae R, Sekine T, Tagami T, et al. Rapidly progressive brain atrophy in septic ICU patients: a retrospective descriptive study using semiautomatic CT volumetry. Crit Care 2021;25(1):411.

[33]. Gu W, Zhong J, Lyu C, et al. An approach for the emergency diagnosis and treatment of sepsis-associated encephalopathy in elderly individuals: a literature review. World journal of emergency medicine 2025;16(5):415-22.