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RESEARCH ARTICLE

Temporal increase in the endothelial activation and stress index before brain death

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Brain death (BD) is accompanied by systemic inflammation and endothelial dysfunction, but temporal changes in endothelial injury during progression to BD remain insufficiently characterized. This study aimed to evaluate serial changes in the Endothelial Activation and Stress Index (EASIX) during the clinical course leading to BD. This retrospective, single-center study included patients diagnosed with BD in the intensive care unit (ICU) between January 2019 and June 2025. EASIX, calculated from lactate dehydrogenase (LDH), serum creatinine, and platelet count, was assessed at ICU admission, 24 hours before BD, 12 hours before BD, and at BD diagnosis. Temporal differences were analyzed using the Friedman test, followed by Wilcoxon signed-rank tests with Bonferroni adjustment. Of 222 patients diagnosed with BD, 52 met the inclusion criteria. EASIX values differed significantly across the four time points ($P < 0.001$), with significant differences observed between ICU admission and BD diagnosis and between 24 and 12 hours before BD. These findings indicate that EASIX increases during the clinical course leading to BD and may reflect progressive systemic endothelial activation and worsening critical illness rather than a BD-specific process. Prospective comparative studies are needed to validate its clinical utility.

Keywords: Brain death, EASIX, endothelial dysfunction, critical illness.

Introduction

Brain death (BD), also known as neurological death, is a clinical state characterized by the irreversible cessation of all brain functions, including those of the brainstem. BD is widely accepted as a definitive criterion for death from medical, ethical, and legal standpoints. It commonly arises from traumatic brain injury (TBI), spontaneous intracerebral hemorrhage, or hypoxic-ischemic encephalopathy [1, 2]. Patients with BD are frequently monitored in intensive care units (ICUs) and often develop multiorgan dysfunction driven by complex pathophysiological processes. The deterioration of organ function is exacerbated by systemic inflammation, hemodynamic instability, and microvascular dysfunction [3].

A growing body of evidence indicates that catastrophic brain injury and progression to BD are associated with significant systemic inflammation and endothelial activation [4, 5]. Endothelial cell activation triggers the release of adhesion molecules and proinflammatory mediators, initiating microthrombotic processes that impair tissue perfusion [6]. Endothelial dysfunction not only affects brain tissue but also impacts systemic circulation and other organs, directly influencing patient mortality and organ donation eligibility [7]. Therefore, early identification of parameters reflecting endothelial activation in patients at risk of BD is crucial for clinical assessment and monitoring.

Endothelial Activation and Stress Index (EASIX) is a recently identified and increasingly utilized noninvasive biomarker calculated from serum lactate dehydrogenase (LDH), platelet count, and serum creatinine levels [8]. Initially, the EASIX score was employed to predict endothelial damage and complications following allogeneic hematopoietic stem cell transplantation. However, recent findings have demonstrated its efficacy in predicting prognosis in patients with sepsis, SARS-CoV-2 infection, and those requiring intensive care [9, 10]. Elevated EASIX scores reflect the severity of systemic inflammation and endothelial injury, correlating with an increased risk of mortality and organ failure.

Nevertheless, the clinical association of the EASIX score in patients diagnosed with BD remains underexplored. Further research is necessary to evaluate the correlation between this score and the clinical progression of patients with BD. This study retrospectively evaluated the temporal changes and clinical association of EASIX during the progression to BD in critically ill patients, drawing from a cohort of 222 patients diagnosed with BD and monitored in ICUs.

Materials and methods

This retrospective study was approved by the Scientific Ethics Committee of Antalya Training and Research Hospital, Health Sciences University (Date: 07/03/2025, No: 11/17), and conducted in accordance with the ethical standards of the Declaration of Helsinki. Due to the retrospective nature of

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the study, which utilized previously collected and anonymized clinical data from ICU patients diagnosed with BD, the institutional ethics committee waived the requirement for informed consent.

Patients diagnosed with BD in the ICU between January 2019 and June 2025 were included. Exclusion criteria comprised an ICU stay of less than 48 h, unavailable or incomplete data, acute or chronic kidney disease requiring renal replacement therapy, or chronic kidney disease deemed to substantially affect serum creatinine levels.

A retrospective review of patient information was conducted using physical files and the hospital's electronic information system. Comprehensive demographic data, including age and gender, were compiled. Laboratory findings, specifically white blood cell count, platelet count, hemoglobin, serum creatinine, and LDH levels, were meticulously documented. Initial admission diagnoses leading to BD (e.g., intracranial hemorrhage, ischemia, intracranial mass) were recorded. Acute Physiology and Chronic Health Evaluation II (APACHE II) and Glasgow Coma Scale (GCS) scores were documented at ICU admission. The EASIX score was calculated using the following formula [8]: EASIX = (LDH [U/L] × creatinine [mg/dL]) / platelet count (10^9/L).

Before BD assessment, all diagnostic prerequisites were confirmed, including a known irreversible catastrophic brain injury and the exclusion of reversible causes of coma, such as hypothermia, severe metabolic or endocrine disturbances, intoxication, and the effects of sedative or neuromuscular blocking agents. BD was established through a comprehensive neurological examination demonstrating deep coma, absence of all brainstem reflexes, and apnea confirmed by a standardized apnea test. When apnea testing could not be safely completed or the clinical examination was not fully assessable, ancillary tests were performed in accordance with national guidelines. The diagnosis was confirmed by legally authorized physicians, as required by national regulations. For this study, the officially documented time of BD declaration in the medical record was designated as T4, while T2 and T3 were retrospectively defined as 24 and 12 h before T4, respectively. BD was determined in accordance with the Republic of Türkiye Ministry of Health Brain Death Diagnosis Guide and contemporary international consensus recommendations [11, 12].

For each predefined study time point (T1, T2, T3, and T4), the laboratory measurement closest to the target time was used for EASIX calculation. If multiple measurements were available within the same time window, the value closest to the predefined reference time was selected. Only patients with complete LDH, serum creatinine, and platelet measurements at all four predefined time points were included in the analysis.

Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) (version 25.0, Armonk, NY: IBM Corp.). Data were summarized using descriptive statistics (n [%], arithmetic mean ± SD, or median [IQR]). The Kolmogorov-Smirnov test assessed the normality of continuous variables. A P-value less than 0.05 was considered statistically significant.

The Shapiro-Wilk test indicated a non-normal distribution of EASIX values at each time point, necessitating the use of non-parametric methods for repeated-measures comparisons. The Friedman test was employed to compare EASIX values across the four time points (T1, T2, T3, T4). If the Friedman test indicated a statistically significant overall difference, post hoc pairwise comparisons were performed using the Wilcoxon signed-rank test. To mitigate the increased risk of Type I error from multiple comparisons, Bonferroni-adjusted P-values were calculated for post hoc analyses, with adjusted P-values < 0.05 considered statistically significant. Effect sizes for the Wilcoxon signed-rank tests were calculated using the formula $r = |Z|/\sqrt{N}$, where r values of approximately 0.10, 0.30, and 0.50 were interpreted as small, medium, and large effects, respectively. Given the non-normal distribution of the data, continuous variables were reported as medians (25th–75th percentiles).

Results

Between January 2019 and June 2025, 222 patients were diagnosed with BD in the ICUs of our institution. Of these, 132 patients were excluded due to incomplete data, 9 had an ICU stay of less than 48 h, and 29 met the predefined renal exclusion criteria (acute or chronic kidney disease requiring renal replacement therapy, or chronic kidney disease significantly affecting serum creatinine). Consequently, 52 patients were included in the final analysis (Figure 1).

The median age of the patients was 51.5 years. Patients exhibited elevated APACHE II scores (26 ± 6.2) and reduced GCS scores (median 5). Intracranial hemorrhage was the most common admission diagnosis, accounting for 69.2% of the cohort. The median ICU length of stay was five days (see Table 1).

EASIX values demonstrated significant differences across the four predefined time points (Figure 2). Bonferroni-adjusted post hoc analysis revealed significant pairwise differences between T1 and T4, and between T2 and T3 (Table 2).

Discussion

This retrospective study of patients diagnosed with BD indicates that BD involves not only neurological damage but also significant systemic endothelial activation [6]. A statistically significant increase in the EASIX score was observed during the clinical course leading to BD. Bonferroni-adjusted post hoc analysis revealed significant differences between T1 and T4, and between T2 and T3.

Sudden endothelial activation, occurring within 72 h of brain injury, results from multiple pathophysiological mechanisms. During this period, accumulated oxidative stress elevates reactive oxygen species (ROS) production. ROS accumulation is crucial to secondary brain injury progression, as it triggers an inflammatory response, induces apoptosis and autophagy, and disrupts blood-brain barrier (BBB) integrity [13]. The acute phase response is characterized by rapid cytokine release, complement activation, and early BBB breakdown [14]. Existing

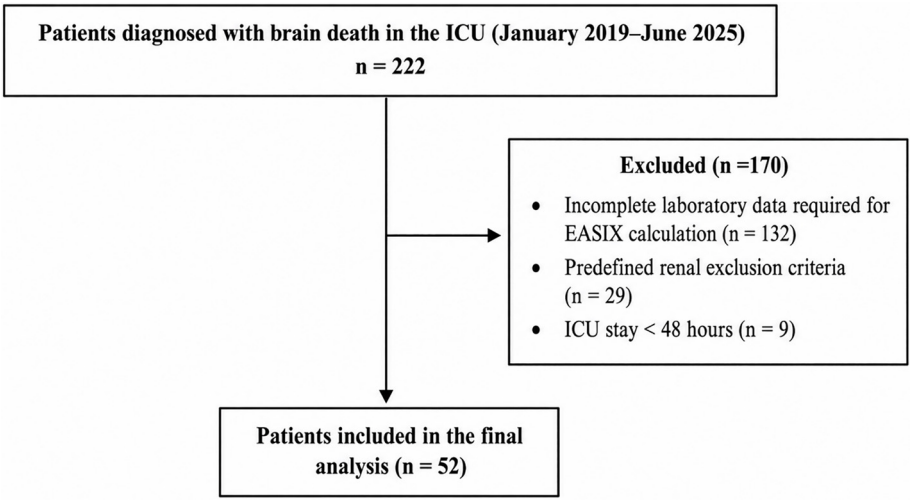


Figure 1. Flowchart of patient selection.

Table 1. Demographic characteristics of the study population

	Included patients *n* = 52	Excluded patients *n* = 170	*P* value
Gender F / M *n* (%)	25 / 27 (48.1 / 51.9)	65 / 105 (38.2 / 61.8)	0.206
Age years median (IQR)	52 (15–63)	54 (38–69)	0.051
APACHE II median (IQR)	20 (14–26)	19 (14–25)	0.810
Glasgow Coma Scale median (IQR)	5 (3–10)	5 (3–7)	0.330
Diagnosis *n* (%)			
Intracranial hemorrhage	36 (69.2)	108 (63.5)	
Ischemia	9 (17.3)	40 (23.5)	0.746
Tumor	4 (7.7)	8 (4.7)	
Intoxication	2 (3.9)	8 (4.7)	
Infection	1 (1.9)	6 (3.5)	
Comorbidities *n* (%)			
Hypertension	19 (36.5)	69 (40.6)	0.601
Diabetes mellitus	10 (19.2)	49 (28.8)	0.171
Coronary artery disease	11 (21.2)	34 (20)	0.856
Malignancy	6 (11.5)	9 (5.3)	0.116
Neurological disease	4 (7.7)	18 (10.6)	0.541
Respiratory disease	2 (3.9)	19 (11.2)	0.114
Other	3 (5.8)	21(12.4)	0.181
Intensive care unit days median (IQR)	5 (4–8)	4 (2–7)	**0.001**

Data are presented as *n* (%), mean ± SD, or median (IQR). **Abbreviations:** APACHE II, Acute Physiology and Chronic Health Evaluation II; F, female; IQR, interquartile range; M, male; n, number; SD, standard deviation.

literature highlights this period as a critical window for neurological prognosis, particularly in conditions such as TBI, stroke, or subarachnoid hemorrhage. Within 48–72 h post-injury, inflammation persists, and BBB dysfunction continues. Neuroinflammation in this phase is marked by microglial activation, astrocyte transition to a reactive phenotype, and endothelial cell dysfunction. Despite heightened BBB permeability and substantial microglial activation in perihematomal regions, limited spatial overlap between these processes suggests independent or partially distinct mechanisms [15]. In the subsequent phase, the persistence of endothelial dysfunction and potential for delayed complications are notable. This late phase's microvascular integrity disruption can lead to continued cerebral edema, delayed ischemic lesions, and limited neurological recovery [16].

Evaluating the parameters comprising the EASIX score, increased LDH levels are attributed to greater release from endothelial cells, platelets, and leukocytes following vascular endothelial damage [17, 18]. Conversely, elevated serum creatinine levels indicate adverse renal function due to renal endothelial dysfunction. Furthermore, a decrease in platelet count may be partially associated with endothelial damage and complement system activation [19]. A recent study also demonstrated a significant association between high EASIX scores and

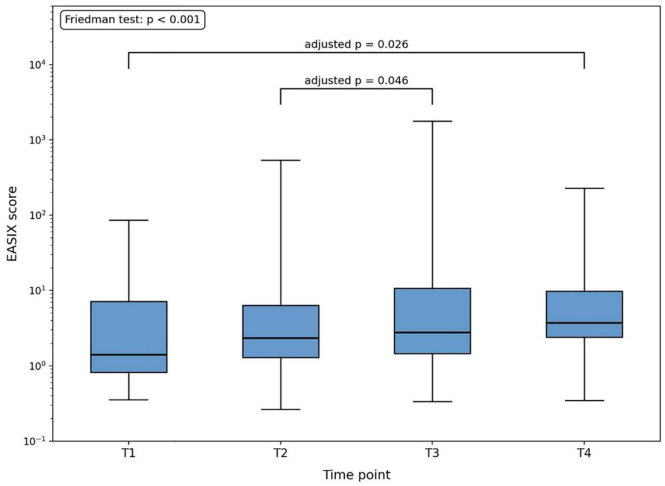


Figure 2. Temporal changes in the Endothelial Activation and Stress Index during progression to brain death. Box-and-whisker plots show Endothelial Activation and Stress Index values at intensive care unit admission (T1), 24 hours before brain death diagnosis (T2), 12 hours before brain death diagnosis (T3), and at the time of brain death diagnosis (T4) in 52 patients. The horizontal line within each box represents the median, the box represents the interquartile range, and the whiskers extend to 1.5 times the interquartile range; observations beyond the whiskers are displayed as individual outliers. Values are presented on a logarithmic scale. Endothelial Activation and Stress Index values differed significantly across the four time points according to the Friedman test ($P < 0.001$). Post hoc Wilcoxon signed-rank tests with Bonferroni adjustment showed significant differences between T1 and T4 (adjusted $P = 0.026$) and between T2 and T3 (adjusted $P = 0.046$). Adjusted P values < 0.05 were considered statistically significant. **Abbreviations**: EASIX, Endothelial Activation and Stress Index; IQR, interquartile range; n, number of patients; T1, intensive care unit admission; T2, 24 hours before brain death diagnosis; T3, 12 hours before brain death diagnosis; T4, time of brain death diagnosis.

Table 2. Pairwise comparisons of EASIX values between study time points, following an overall Friedman test

Comparison	*n*	Median (IQR) – earlier time point	Median (IQR) – later time point	Z	*r* (effect size)	*P* (unadjusted)	*P* (Bonferroni)
T1–T2	52	T1: 1.41 (0.82–7.15)	T2: 2.35 (1.29–6.40)	–1.27	0.18	0.206	1.000
T1–T3	52	T1: 1.41 (0.82–7.15)	T3: 2.78 (1.46–10.68)	–2.27	0.31	0.023	0.140
T1–T4	52	T1: 1.41 (0.82–7.15)	T4: 3.74 (2.40–9.81)	–2.85	0.40	0.004	**0.026** *
T2–T3	52	T2: 2.35 (1.29–6.40)	T3: 2.78 (1.46–10.68)	–2.67	0.37	0.008	**0.046** *
T2–T4	52	T2: 2.35 (1.29–6.40)	T4: 3.74 (2.40–9.81)	–2.58	0.36	0.010	0.060
T3–T4	52	T3: 2.78 (1.46–10.68)	T4: 3.74 (2.40–9.81)	–1.16	0.16	0.247	1.000

Pairwise post hoc comparisons were conducted using the Wilcoxon signed-rank test, with Bonferroni-adjusted *P* values reported. Statistical significance was set at an adjusted *P* value of less than 0.05. **Abbreviations:** EASIX, Endothelial Activation and Stress Index; IQR, interquartile range; n, number of patients; r, effect size; T1, intensive care unit admission; T2, 24 hours before brain death; T3, 12 hours before brain death; T4, time of brain death diagnosis; Z, standardized Wilcoxon signed-rank test statistic.

mortality in TBI cases [20]. The efficacy of EASIX in predicting prognosis in both hematological malignancies and critical illness has been emphasized in recent studies [7, 8]. In this study, a significant increase in EASIX scores from baseline to 24 h before and at the time of BD diagnosis is consistent with the literature, indicating exacerbated endothelial activation. Consequently, it is hypothesized that the EASIX score may serve as a marker of endothelial activation in critically ill patients progressing to BD.

Factors leading to BD are influenced by several variables, including patient age, comorbidities, and regional healthcare access. According to existing literature, the most prevalent etiologies of BD are TBI, intracerebral hemorrhage, and hypoxic-ischemic encephalopathy. However, high-energy traumas, such as motor vehicle accidents and falls from heights, are more common in younger age groups, whereas spontaneous intracerebral hemorrhages and malignant cerebrovascular events are more common in older age groups [21]. Hypoxic-ischemic encephalopathy following cardiac arrest accounts for a significant proportion of non-traumatic BD cases [22, 23]. Furthermore, the increasing frequency of endovascular neurointerventions in some countries has been associated with a rise in BD cases [24], indicating a need for enhanced surveillance of advanced interventional neurological treatments to ensure optimal complication management. Central nervous system infections are a rare cause of BD [25]. The findings of the present study are consistent with the extant literature. Among hospitalized patients subsequently diagnosed with BD, intracranial hemorrhage, ischemia, and intracranial tumors accounted for approximately 95% of diagnoses. Therefore, early recognition of pathophysiological processes leading to

BD is vital for two reasons: objective assessment of neurological prognosis and facilitation of timely and effective organ donation processes.

The present study has several notable limitations. First, the retrospective, single-center design and relatively small sample size inherently limit the generalizability of the findings. Critically, the study lacked a comparator group of critically ill patients with severe neurological injury who did not progress to BD. Consequently, we could not evaluate the diagnostic and prognostic performance of the EASIX score—such as its sensitivity, specificity, and optimal cutoff values—nor definitively conclude that the observed increase in EASIX is specific to BD rather than a general reflection of critical illness.

Second, a substantial proportion of the initial cohort (132 of 222 patients, 59.5%) was excluded due to missing laboratory data, particularly LDH, which is required to calculate the EASIX score. This high exclusion rate likely introduced selection bias; the included patients may represent a subpopulation that required more intensive monitoring or differed clinically from those excluded.

Third, due to the study's observational design and the absence of a control group, we could not account for potential confounding variables (e.g., sepsis, vasopressor use). Similarly, factors that independently affect the EASIX components, such as hemolysis, blood product transfusions, and liver damage, could not be evaluated. Furthermore, patients with acute or chronic kidney disease requiring renal replacement therapy, or with chronic kidney disease, were excluded because renal dysfunction directly alters creatinine levels. Therefore, the applicability of EASIX in patients with advanced renal failure remains uncertain.

Finally, the study was not designed to assess the incremental value of the composite EASIX score over its individual components, particularly LDH, which may have strongly influenced the observed trends. Future prospective studies with appropriate comparator groups and multivariable analyses are essential to validate the diagnostic utility of the EASIX score and to assess its independent contribution beyond established clinical risk factors and individual laboratory parameters.

Conclusion

In conclusion, the EASIX score increased during the clinical course leading to BD in this selected cohort, potentially reflecting worsening critical illness with progressive systemic endothelial activation rather than a brain-death-specific process. EASIX is a low-cost composite index readily calculable from routine laboratory parameters. These findings suggest that EASIX may represent a candidate marker requiring validation in prospective comparative studies. Further comparative studies are needed to better characterize the temporal behavior of EASIX and its association with disease progression in patients with severe neurological injury.

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Data availability: The data supporting the findings of this study are presented in the article. Additional data may be obtained from the corresponding author upon reasonable request.

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Supplemental data

Graphical abstract

