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C-REACTIVE PROTEIN AS AN INDICATOR OF INFLAMMATION AND INFECTION IN BRAIN-DEAD ORGAN DONORS

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Elevated C-reactive protein (CRP) levels in brain-dead donors (BDDs) may indicate an underlying infectious process or may be related to the pathogenesis of the primary disease and brain death (BD) itself. The **objective** of this study was to assess the prognostic value of CRP levels in detecting infectious complications in BDDs prior to organ and/or tissue procurement. **Materials and methods.** This prospective pilot study included 345 BDDs. Median donor age was 54 years (IQR: 47–62); 218 (63.2%) were men and 127 (36.8%) women. The primary diagnoses leading to BD were: non-traumatic intracranial hemorrhage (n = 220; 63.8%), ischemic brain injury (n = 68; 19.7%), and traumatic brain injury (n = 57; 16.5%). **Results.** CRP levels measured after the first medical examination by the BD consultation were already significantly elevated above reference values, with a median of 176.2 mg/L (IQR: 100.5–276.4) after 18–24 hours. Following the second examination and confirmation of brain death, CRP levels increased further to a median of 271.1 (IQR: 174.1–365.0) mg/L ($\chi^2 = 35.79$, $p < 0.00001$). The most frequently diagnosed infection during donor conditioning was pneumonia, observed in 79 donors (22.9%). Receiver operating characteristic (ROC) analysis was conducted to evaluate the predictive value of CRP levels for pneumonia in potential donors: at stage 1, AUC = 0.633 (SE = 0.04; 95% CI: 0.57–0.69; p = 0.001), with a cutoff point of 295 mg/L (sensitivity 36.9%, specificity 86.3%). At stage 3, AUC = 0.630 (SE = 0.05; 95% CI: 0.55–0.71; p = 0.01), with a cutoff value of 348.6 mg/L (sensitivity 47.7%, specificity 79%). **Conclusion.** Analysis of CRP levels provides a useful tool for detecting pulmonary infections in potential BDDs.

Keywords: C-reactive protein, CRP, brain death, infection, organ donor, transplantation.

INTRODUCTION

Infectious complications in brain-dead organ donors (BDDs) remain a critical concern in transplantation medicine [1, 2]. Studies indicate that approximately 15% of organ transplant recipients develop infections transmitted from BDDs [3]. Such donor-derived infections can significantly compromise transplant outcomes, leading to reduced survival rates for both recipients and grafts [4, 5].

The most reliable approach to detecting infection in BDDs involves bacteriological analyses of suspected infection sites [6, 7]. However, these investigations are not routinely performed in donors who are not suspected of having infectious complications. Unfortunately, the results of such analyses often become available only after the organs have been transplanted to recipients.

A range of laboratory biomarkers, such as acute phase proteins, procalcitonin, and presepsin, are used to facilitate early detection of infection in BDDs [8]. Among these, C-reactive protein (CRP) is the most widely used in clinical practice [9]. CRP is a highly sensitive marker of acute-phase inflammation, capable of rapidly reflecting changes in the severity of inflammatory processes; however, its specificity remains low. Notably, elevated CRP levels in BDDs may result not only from infectious processes but also from destruction of brain cells [9].

At present, few studies have investigated the dynamics of CRP levels in potential BDDs and their relationship to active infection during intensive care management in anesthesiology and intensive care units (ICU) settings [10].

In this regard, the present study aimed to evaluate the prognostic value of CRP levels in detecting infectious complications in BDDs prior to organ and/or tissue procurement.

MATERIALS AND METHODS

This prospective study included 345 potential brain-dead organ and/or tissue donors who underwent intensive care and subsequent conditioning of functional systems in anesthesiology and ICU units between 2020 and 2023. The study protocol was reviewed and approved by the Regional Ethics Committee (Approval No. 1/2020).

The age of donors was 54 (47; 62) years (median and 25%–75% quartiles). Median body weight was 80 kg (IQR: 70–90), median height was 173 cm (IQR: 168–180), and median body mass index (BMI) was 26.3 kg/m^2 (IQR: 24.5–29.3). The study cohort comprised 218 male (63.2%) and 127 female donors (36.8%).

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Potential donors were eligible for inclusion if they met the following criteria:

1. Severe brain injury characterized by a Glasgow Coma Scale score of 3 and a Full Outline of UnResponsiveness (FOUR) scale score of 0, resulting from: nontraumatic intracranial hemorrhage (NICH), ischemic brain injury, including brain infarction (BI) or hypoxic brain injury, and traumatic brain injury (TBI)
2. Completion of a medical consultation confirming brain death.

The exclusion criteria were:

1. Presence of contraindications to organ and/or tissue procurement, including confirmed viral infectious diseases (hepatitis B, hepatitis C, or HIV), malignant neoplasms, or sepsis with evidence of multiple organ failure or dysfunction;
2. Existence of a written statement by the patient or their legal representative declining post-mortem organ donation.

Brain death was diagnosed by a medical council at the healthcare institution where the potential donor was hospitalized. The determination was made in accordance with generally recognized criteria and the applicable regulatory and legal provisions of the Republic of Belarus.

The main causes of brain death in the study cohort were: NICH (n = 220, 63.8%), ischemic BI (n = 53; 15.4%), hypoxic encephalopathy (n = 15, 4.3%), and TBI (n = 57, 16.5%).

The median time from hospital admission to the first medical consultation for confirmation of brain death (BD) was 60 hours (interquartile range: 34–118.3 hours). In 139 potential donors (40.3%), surgical procedures were performed to procure donor organs and/or tissues for transplantation. The median time from hospital admission to initiation of organ and/or tissue procurement surgery was 111 hours (interquartile range: 76.1–161 hours) (Fig. 1).

During intensive care and conditioning of functional systems, the condition of each potential donor was assessed using both laboratory and instrumental diagnostic methods. All donors underwent chest X-rays (at admission, upon BD confirmation, and upon suspicion of pulmonary pathology), abdominal and renal ultrasound, and echocardiography. All standard laboratory evaluations were performed daily, including complete blood count, urinalysis, biochemical profile test, coagulation tests, and electrolyte and arterial blood acid-base composition analysis. Additionally, CRP levels were measured daily using the immunoturbidimetric method, with reference serum values of 0–5 mg/L.

Laboratory and instrumental data were analyzed at three stages: stage 1 (after initial examination by the consultation committee to confirm BD), stage 2 (18–24 hours after the first examination), and stage 3 (after the second examination and the official confirmation of BD).

Statistical analysis was performed using Statistica 12.0 (StatSoft Inc., USA). Normality of data distribution was assessed using the Shapiro–Wilk test. For normally distributed data, results were expressed as mean ± standard deviation (M ± SD). For non-normally distributed data, results were presented as median with lower and upper quartiles (Me [LQ; UQ]).

Comparisons between independent groups were conducted using the Mann–Whitney U test, while comparisons between dependent groups employed the Wilcoxon matched pairs test or, for three or more groups, Friedman's test in conjunction with Kendall's coefficient of concordance. Where multiple comparisons were performed, p-values were adjusted using the Bonferroni correction.

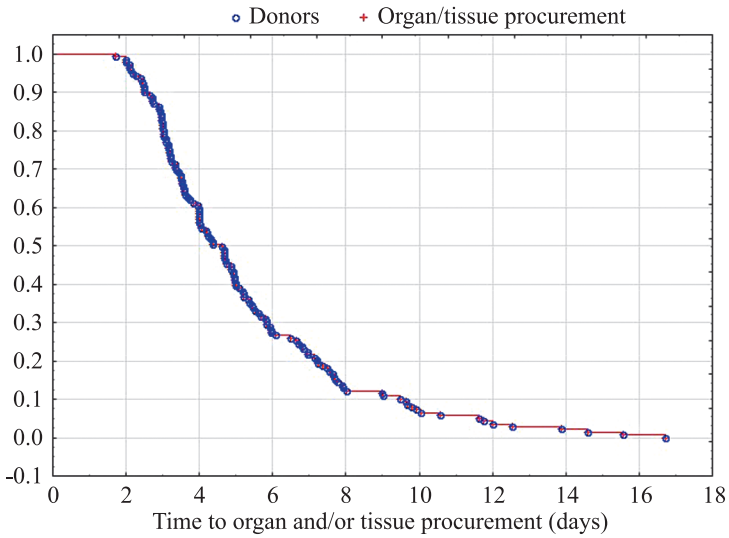

Fig. 1. Kaplan–Meier curve illustrating the time from donor arrival to the initiation of organ and/or tissue procurement in deceased donors

Correlation analysis was carried out using Spearman's rank correlation coefficient (R). Statistical significance was set at $p < 0.05$.

RESULTS

CRP values at all study stages are presented in Table 1. At stage 1, median CRP level was 176.2 (100.5–276.4) mg/L; at stage 2, it increased to 232.9 (137.2–329.0) mg/L; and at stage 3, it reached 271.1 (174.1–365.0) mg/L. This increase across stages was statistically significant ($\chi^2 = 35.79$, $p < 0.00001$; Friedman ANOVA with Kendall's coefficient of concordance). Pairwise comparisons revealed significant differences between all stages: stage 1 *vs* stage 2 ($p = 0.00001$), stage 2 *vs* stage 3 ($p = 0.0009$), and stage 1 *vs* stage 3 ($p = 0.00001$) (Wilcoxon matched pairs test).

When CRP levels were compared between brain-dead donors without organ or tissue procurement and those who underwent explantation, the following results were obtained: stage 1 – 173.2 (105.2–276.4) mg/L *vs* 184.2 (95.4–275.9) mg/L; stage 2 – 233.2 (169.5–324.4) mg/L *vs* 224.3 (132.5–330.0) mg/L; stage 3 – 303.4 (229.2–370.2) mg/L *vs* 267.8 (164.4–362.1) mg/L. These differences were not statistically significant at any stage ($p > 0.1$; Mann–Whitney U test).

We also analyzed laboratory markers of the inflammatory response, including procalcitonin levels, at each stage of the study (Table 1).

Correlation analysis between CRP levels and other laboratory markers of inflammatory response, including procalcitonin, showed the strongest positive correlation with erythrocyte sedimentation rate (ESR) at all stages of the study ($R = 0.38$, $p = 0.0004$; $R = 0.46$, $p < 0.00001$; and $R = 0.27$, $p = 0.01$ at stages 1, 2, and 3, respectively). A weak but statistically significant positive correlation was also observed between CRP and procalcitonin levels ($R = 0.30$, $p = 0.01$; $R = 0.38$, $p = 0.003$ at stages 1 and 2, respectively). No significant correlation was found between CRP levels and leukocyte differential parameters.

Pneumonia was the most common infectious complication among potential donors during conditioning, occurring in 79 cases (22.9%). Importantly, the presence of an infectious process does not preclude organ and tissue procurement, provided there is evidence of clinical improvement under antibacterial therapy and no signs suggestive of sepsis.

A comparison of leukocyte differential indicators and acute-phase protein levels between potential donors with and without pneumonia revealed no statistically significant differences, except for CRP values (Table 2). CRP levels were significantly higher in donors with pneumonia compared to those without, and this difference was observed at all stages of the study.

Receiver operating characteristic (ROC) analysis was conducted to evaluate the predictive value of CRP levels at stages 1 and 3 for the presence of pneumonia in potential donors (Fig. 2). At stage 1, the area under the curve (AUC) was 0.633 (SE = 0.04, 95% CI: 0.57–0.69, $p = 0.001$). The cutoff value for CRP at this stage was 295 mg/L, yielding a sensitivity of 36.9% and a specificity of 86.3% for predicting pneumonia after the first consultation to confirm BD.

At stage 3, after brain death was confirmed, the AUC was 0.63 (SE = 0.05, 95% CI: 0.55–0.71, $p = 0.01$). The CRP cutoff value at this stage was 348.6 mg/L, corresponding to a sensitivity of 47.7% and a specificity of 79%.

DISCUSSION

In this study, we evaluated CRP levels along with several other inflammatory response markers in BDDs across three stages of observation. A statistically significant increase in both CRP and ESR levels was observed at all stages, reflecting the extent of the non-infectious inflammatory response associated with cellular and tissue injury following severe brain injury and subsequent brain death. However, CRP levels did not influence the likelihood of organ or tissue procurement from potential donors.

Table 1

Leukocyte differential, ESR, and procalcitonin indicators at different stages of the study*

	Leukocytes ($\times 10^9$/L)	Neutrophils ($\times 10^9$/L)	Lymphocytes ($\times 10^9$/L)	Band neutrophils (%)	ESR (mm/h)	CRP (mg/mL)	Procalcitonin (ng/mL)
Stage 1	12.9 (9.8; 18)	10.5 (9.2; 14.8)	1.8 (1.2; 2.4)	8 (5; 14)	22 (12; 35)	176.2 (100.5; 276.4)	2.1 (0.6; 7.9)
Stage 2	15.1 (11; 18.6)	11.3 (8.1; 15.3)	1.5 (0.9; 2.2)	11 (6; 18.5)	30 (16; 45)	232.9 (137.2; 329)	2 (0.6; 5.1)
Stage 3	13.9 (10.1; 18.2)	10.5 (7.6; 14.6)	1.5 (1.1; 2.1)	13 (6; 21)	27 (16; 46)	271.1 (174.1; 365)	2.1 (0.7; 5.8)
ANOVA χ^2; p*	3.12; 0.21	3.15; 0.21	0.31; 0.86	3.06; 0.22	44.09; <0.00001	35.79; <0.00001	0.14; 0.93

* – comparison of indicators (Friedman ANOVA and Kendall Coeff). ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

Only a limited number of studies have investigated inflammatory response markers and acute-phase protein levels in patients with irreversible brain injury and in potential organ donors [10–12]. Consistent with our findings, these studies report a marked rise in CRP levels during the first 3–4 days after severe brain injury, with further elevation upon confirmation of BD [12]. The rapid surge in CRP may be attributed to its expression not only in hepatocytes but also in neurons and glial cells following brain injury [13].

In this study, we focused only on laboratory indicators of systemic inflammatory response syndrome , as clinical parameters such as heart rate and respiratory rate cannot be reliably interpreted in BD patients. Changes in leukocyte profile and procalcitonin levels across all study stages were not statistically significant. Notably, the study excluded BDDs with laboratory evidence of sepsis.

Given that CRP levels in BDDs are often dozens of times higher than reference values and continue to rise during conditioning, its diagnostic utility for identifying infectious complications remains uncertain. However, in our cohort, donors with pulmonary infections consistently demonstrated significantly higher CRP levels at all study stages. In contrast, procalcitonin and leukocyte profile changes did not reach statistical significance. Although the prognostic CRP thresholds determined by ROC analysis exhibited fairly low sensitivity, they may still serve as a useful tool for detecting localized infections in donors and for identifying cases warranting mandatory bacteriological testing.

Limitations of the study. It is important to acknowledge that CRP elevation in BDDs is influenced by several factors not examined in this study. These include duration of donor conditioning, interval since BD was confirmed, primary cause of brain injury (e.g., TBI), and any surgical interventions performed prior to organ procurement.

Therefore, CRP levels in potential organ and/or tissue donors may serve as a quantitative marker not only of systemic inflammatory response and organ injury fol-

Table 2

Leukocyte differential, ESR, and procalcitonin indicators in patients with and without pneumonia at different stages of the study*

		Leukocytes ($\times10^9$/L)	Neutrophils ($\times10^9$/L)	Lymphocytes ($\times10^9$/L)	Band neutrophils (%)	ESR (mm/h)	CRP (mg/mL)	Procalcitonin (ng/mL)
Without pneumonia, n = 266 (77.1%)	Stage 1	12.5 (9.7; 17.8)	11.1 (9.9; 14.8)	1.8 (1.3; 2.5)	8 (5; 12)	21 (11; 35)	164.7 (90.1; 255.5)	2.1 (0.7; 7.6)
	Stage 2	15.2 (11.4; 18.3)	12 (8.6; 15.3)	1.5 (1; 2)	10 (6; 18)	27.5 (15.5; 43)	215.5 (129.8; 294.1)	2.1 (0.5; 4.1)
	Stage 3	14 (10.5; 16.9)	10.8 (7.9; 13.8)	1.4 (1.1; 1.8)	11 (6; 19)	25 (16; 45)	244.2 (155.5; 335.6)	2.2 (0.7; 6.8)
With pneumonia, n = 79 (22.9%)	Stage 1	13.8 (10.8; 18.5)	9.7 (7.6; 16.3)	1.4 (0.9; 2.3)	11 (6; 19)	27.5 (15; 40)	235.5 (141; 350)	1 (0.2; 20)
	Stage 2	13.6 (10.4; 19.1)	9.9 (7.1; 16.1)	1.2 (0.9; 3.5)	14 (9; 21)	35 (16; 50)	297.4 (165.4; 386.4)	1.8 (0.9; 14.7)
	Stage 3	11.3 (9.8; 19.4)	9.8 (6.9; 14.7)	1.8 (0.8; 3)	16 (8; 22)	39 (17; 50)	314 (238.7; 393.2)	1.8 (1; 3.2)

* Comparison of CRP levels between two groups using the Mann–Whitney U test: Stage 1 – p = 0.0002; Stage 2 – p = 0.009; Stage 3 – p = 0.01. ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

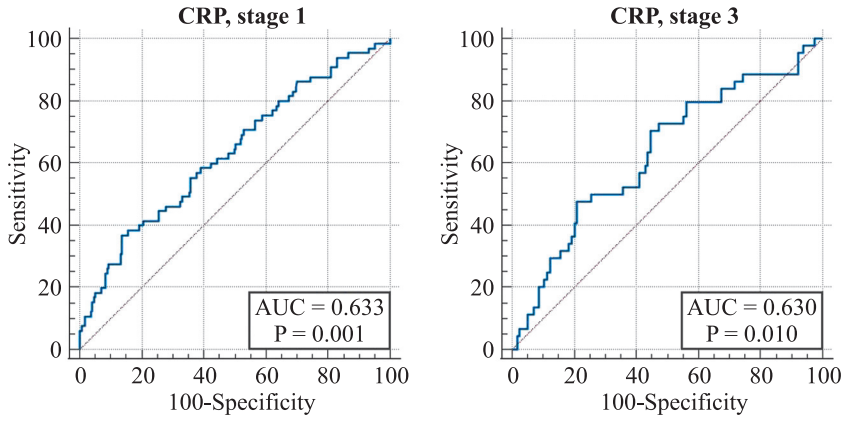

Fig. 2. ROC curves for CRP levels in relation to the presence of pneumonia in potential donors at different stages of the study

lowing severe brain damage and death, but also a criterion for the addition of an infectious process. Regular CRP monitoring during the conditioning period could aid in the early detection and management of infectious complications, improving transplant outcomes.

CONCLUSION

1. CRP levels in potential donors increases during brain death and conditioning of functional systems: stage 1 – 176.2 (100.5; 276.4) mg/L, stage 2 – 232.9 (137.2; 329) mg/L, and stage 3 – 271.1 (174.1; 365) mg/L ($\chi^2 = 35.79$, $p < 0.00001$).
2. Analysis of CRP levels allows the detection of an infectious process in the lungs of potential BDDs. Threshold values were >295 mg/L after the first consultation and >348.6 mg/L following BD confirmation, serving as potential cut-off points for infection screening.

The authors declare no conflict of interest.

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