PROSPERITAS VESTRA FINIS NOSTRA!

AUTOREFERAT

Scientific Specialty "Anesthesiology and Intensive Care" – 03.01.38

The dissertation consists of a total of 132 pages, illustrated with 45 figures and 52 tables. The bibliography contains 124 titles, of which 5 are in Cyrillic and 119 in Latin script. The research, reviews, laboratory tests, and monitoring were carried out in the facilities of University Hospital "St. Marina", Varna. The doctoral candidate holds the position of "assistant physician" in the Department of Anesthesiology and Intensive Care at University Hospital "St. Marina" - Varna and the Department of Anesthesiology, Emergency, and Intensive Care Medicine at the Medical University of Varna. The dissertation was discussed, accepted, and directed for defense before a scientific jury by the

Departmental Council of the Department of Anesthesiology, Emergency, and Intensive Care Medicine at MU "Prof. Dr. Paraskev Stoyanov," Varna with protocol No. 4/14.05.2024.

The public defense of the dissertation will be held on 30.07.2024 online before a scientific jury consisting of:

Internal Members:

- Prof. Dr. Viliyan Hristov Platikanov, PhD - Chair
- Prof. Dr. Nikola Yordanov Kolev, PhD, DSc - Reviewer

Reserve Internal Member:

- Prof. Dr. Deyan Anakievski, PhD

External Members:

- Assoc. Prof. Dr. Georgi Angelov Pavlov, PhD
- Prof. Dr. Kamelia Todorova Tsvetanova, PhD, DSc - Reviewer
- Assoc. Prof. Dr. Teodora Nedeva Sherbanova, PhD

Reserve External Member:

- Assoc. Prof. Dr. Lyubomir Stefanov Bakalivanov, PhD

The defense materials are available in the Scientific Department and are published on the website of MU - Varna. Note! The numbering of figures and tables does not match that in the dissertation!

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Abbreviations

ADH – antidiuretic hormone
AQP – aquaporin
ATP – adenosine triphosphate
ICP – intracranial pressure
EEG – electroencephalogram
ECG – electrocardiogram
ECF – extracellular fluid

ABG – acid-base gas
CT – computed tomography
MRA – magnetic resonance angiography
PTH – parathyroid hormone
RAAS – renin-angiotensin-aldosterone system
MAP – mean arterial pressure)
COPD – chronic obstructive pulmonary disease
cAMP – cyclic adenosine monophosphate
CVP – central venous pressure
CNS – central nervous system
CCN - Craniocerebral Nerve
ACE – angiotensin-converting enzyme
ANP – atrial natriuretic peptide
AV-block – atrioventricular block
CBF – cerebral blood flow
CBV – cerebral blood volume
FGFR – fibroblast growth factor receptor
GCS – Glasgow coma scale
IL – interleukin
NMDA – N-methyl-D-aspartate
NKCC2 – Na-K-Cl cotransporter 2
PaCO2 – partial pressure of carbon dioxide
ROMK – renal outer medullary potassium channel
TRPV1 – transient receptor potential vanilloid 1
TTKG – transtubular potassium gradient
2,3-DPG – 2,3-diphosphoglycerate
99mTc-HMPAO – technetium-99m-hexamethylpropyleneamine oxime

I. Introduction

Brain death is a state of complete and irreversible cessation of all brain functions, including the brain stem, while maintaining circulation in the rest of the body. Causes can include traumatic brain injuries, cerebrovascular incidents, anoxia, infectious or neoplastic processes. The percentage of patients with severe primary or secondary brain damage developing brain death ranges between 50% and 65%. They represent a major potential source of organs from cadaveric donors (Guide to the Quality and Safety of Organs for Transplantation, 2022).

Against the backdrop of an ever-increasing need for organ donors, Bulgaria ranks last among European Union countries in the number of transplants per million population. Alongside refusals of donation by patients or their relatives, the reasons for this statistic include unidentified and unreported potential donors. This necessitates good theoretical and practical training for specialists from various units, easy communication between them, quick assessment of the patient's condition, and an appropriate approach to relatives.

Early recognition and confirmation of brain death are crucial for the success of the donor process. Diagnosing patients includes a clinical examination followed by several instrumental investigations to confirm the results already obtained. After the diagnosis is made, a policy of aggressive donor management is initiated. Organ-protective therapy aims to ensure optimal organ perfusion and preserve them in the best possible condition until explantation.

Disrupted central regulation of the cardiovascular system, respiration, baroreceptors, chemoreceptors, and the hypothalamic-pituitary axis observed in brain death leads to typical hemodynamic changes occurring in two main phases. The agonal phase, also known as the "catecholamine storm," begins immediately before brain death and aims to ensure optimal cerebral and coronary perfusion pressure. It is followed by the gradual disappearance of central sympathetic adrenergic regulation, resulting in a complete and irreversible loss of overall brain function.

Approximately 80% of organ donors with brain death exhibit damage to the posterior pituitary lobe, leading to the development of diabetes insipidus with changes in water-electrolyte balance, hypovolemia, and circulatory instability. This results in hypovolemia, hyperosmolarity, hypernatremia, hypokalemia, hypomagnesemia, hypocalcemia, and hypophosphatemia.

Multi-organ involvement in organ donors with brain death presents a significant challenge for specialists working in intensive care units. This motivated us to conduct the present study on changes in water-electrolyte balance and their correction, aiming to provide adequate care and increase the number and quality of transplanted patients.

II. Aim and Objectives

Aim

The aim of our study is to identify changes in the water-electrolyte balance in organ donors with brain death, the causes of these changes, and the methods for their correction in the intensive care unit.

Objectives

To achieve this aim, we set the following objectives:

1. Identify clinical cases of patients who have reached brain death at University Hospital "St. Marina" EAD, Varna, for the period from January 1, 2014, to December 31, 2020.
2. Determine the types and compare the frequency of changes in the water-electrolyte balance occurring in patients in the formed sample.
3. Identify the types and compare the frequency of causes leading to changes in the water-electrolyte balance in patients in the formed sample.
4. Identify the types and compare the frequency of use of various medications and techniques for correcting changes in the water-electrolyte balance applied to patients in the formed sample.
5. Propose an algorithm for correcting the water-electrolyte balance in potential organ donors with brain death.

III. Materials and Methods

1. Materials and Study Design

The study described is retrospective, observational, and monocentric. It was conducted by a team from the Clinic of Anesthesiology and Intensive Care at University Hospital "St. Marina" EAD, Varna, with the principal investigator being the dissertation author. The study was carried out within the structures of University Hospital "St. Marina" EAD, Varna, and it encompasses clinical cases of patients who experienced brain death between January 1, 2014, and December 31, 2020. The study was approved by

the Ethics Committee for Scientific Research (ECSR) No. 121/06.10.2022 at the Medical University "Prof. Dr. Paraskev Stoyanov" - Varna (Appendix No. 1).

The study focuses on patients who experienced brain death and were managed as potential organ donors. Its objective is to establish changes in water-electrolyte balance and their correction in the intensive care setting.

2. Inclusion Criteria

The team established the following inclusion criteria for patients in the study:

- Patients above 18 years of age.
- Patients who experienced brain death between January 1, 2014, and December 31, 2020.

3. Exclusion Criteria

The team established the following exclusion criteria for patients from the study:

- Individuals under 18 years of age.
- Pregnant patients.

4. Process of Subject Selection in the Study

After explicit written permission from the Executive Director of University Hospital "St. Marina" EAD, the Statistics Department provided a list of patients coded in the hospital system as brain death cases for the study period. The Hospital Archive provided the complete medical histories of these patients. Upon document analysis, cases that did not meet the inclusion criteria were excluded from further analysis. The final study included 73 patients diagnosed with brain death, with each of them being considered as an individual case in the study.

5. Definitions Used

From the literature review, it was clarified that there are no universally accepted definitions for some concepts related to changes in water-electrolyte balance. The definitions adopted for this specific study are as follows: (Definitions provided)

6. Methods

6.1. Documentary Method

Information regarding demographic characteristics (gender and age), clinical characteristics (coexisting chronic conditions, acute-onset conditions), water-electrolyte balance indicators (Na^+, K^+, Cl^-, Ca^{2+}, Mg^{2+}, P), techniques, and medications used for their control was collected for all patients included in the study. All data from the study were obtained through processing and analysis of information from

documentary sources – complete medical histories of each patient, discharge summaries related to coexisting chronic conditions, intensive care unit records, laboratory and imaging results, journals. Legal provisions regarding the protection of personal data were adhered to during data processing.

6.2. Clinical Methods

A brief neurological examination, Glasgow Coma Scale assessment, and clinical examination to establish brain death were conducted for all patients. The latter consisted of the above-mentioned tests examining brainstem reflexes:

- Pupillary light reflex

The apnea test was conducted last, following a four-vessel angiography, due to the potential risk of additional nerve damage in the absence of brain death. It was not performed if any of the brainstem reflexes were present.

After diagnosing brain death through the aforementioned clinical examination, patients were transported to the angiography room at University Hospital "St. Marina" - Varna, for a four-vessel cerebral angiography to confirm the diagnosis. Each patient was ventilated using the Philips Trilogy Evo transport ventilator, and non-invasive blood pressure, electrocardiogram (ECG), and pulse oximetry values were monitored.

As described earlier, the gold standard for evaluating cerebral blood flow in patients with brain death is classical four-vessel angiography, as it is not influenced by hypothermia and CNS depressants. The drawbacks include patient transfer outside the intensive care unit, use of nephrotoxic contrast agents, and arterial puncture. The study utilized the Siemens Artis Zee monoplane angiography system equipped with a Leonardo workstation with multifunctional software and 3D reconstruction capability. The angiography system allows for digital subtraction angiography (DSA), road mapping, and rotational angiography.

Evaluation of cerebral blood flow was achieved through femoral artery catheterization and administration of contrast material.

Standard blood tests (complete blood count, biochemical tests, coagulation status, ionogram, blood gas analysis (BGA)), and urine analysis were conducted upon patient hospitalization. After diagnosing brain death, ionogram and BGA were additionally monitored every 6 hours.

ISE (Ion Selective Electrode) method was used to monitor ion levels, which involves an electrochemical method for indirect potentiometry using ion-selective electrodes for Na, K, and Cl. The analysis was performed using the Roche Cobas 6000 analyzer.

A. Roche Cobas 6000 Analyzer *B. Blood Gas Analyzer GEM Premier 300*

Figure 1: Laboratory Equipment for Investigations

6.5. Therapeutic Methods

6.5.1. Mechanical Ventilation

Patients diagnosed with brain death were indicated for mechanical ventilation without the need for sedation to adapt to the ventilator. They were ventilated using the "Drager Evita 2 Dura Ventilator", "Drager Evita XL Ventilator", or "HAMILTON GALILEO VENTILATOR" in SIMV mode, with FiO2 between 0.5 and 1.0 and PEEP between 0 and 5 cmH2O.

6.5.2. Gastric Protection Application

Proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2-antagonists) were used at their respective doses to prevent stress ulcers and gastrointestinal bleeding.

6.5.3. Desmopressin Acetate (Minirin) Administration

In patients who developed diabetes insipidus, desmopressin was administered at a dose of 0.2mg within 24 hours, divided into two equal doses.

6.5.4. Sympathomimetic Agents Application

Dopamine, dobutamine, norepinephrine, or adrenaline were applied either alone or in combination at different doses, determined based on their hemodynamic characteristics, in the majority of patients.

6.5.5. Insulin Application

Insulin was administered in some patients in the form of venous infusion or subcutaneous boluses depending on the blood sugar profile.

6.5.6. Potassium Preparations Application

Potassium preparations were administered to some patients diagnosed with brain death to correct hypokalemia.

6.5.7. Administration of Electrolyte Solutions (ES)

The type and quantity of ES administered to patients were determined based on central venous pressure (CVP) and electrolyte values obtained from laboratory tests.

6.6. Monitoring Methods

6.6.1. Invasive Monitoring

6.6.1.1. Placement of Central Venous Catheter (CVC)

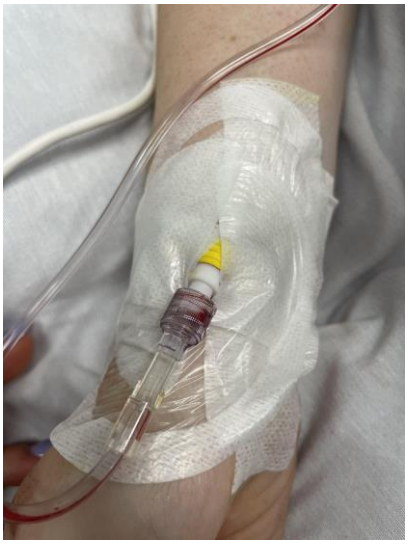
After diagnosing brain death, a central venous catheter is placed, most commonly in the internal jugular vein (right or left depending on patient anatomy), while adhering to all rules of asepsis and antisepsis. The technique used is the Seldinger method under ultrasound control using a specialized single-use kit. This catheterization method allows for high-volume replacement, administration of medications irritating peripheral vessels, and monitoring of CVP.

B. Internal Jugular Vein Puncture *C. Central Venous Catheterization Kit*

Figure 2: Cannulation of the Internal Jugular Vein

6.6.1.2. Placement of Arterial Catheter

The arterial catheter is inserted into the radial artery (on the right or left arm depending on patient anatomy) to measure invasive blood pressure. For this purpose, a specialized single-use kit is used, and the catheter is inserted using the Seldinger method. Before the procedure, an Allen test is performed to assess arterial blood flow to the hand.



6.6.2. Non-invasive Monitoring All patients were monitored using patient monitors and respirators. The parameters monitored included:

- Pulse oximetry
- Standard 3-channel ECG monitoring
- Invasive arterial blood pressure
- Automatic non-invasive blood pressure measurement at 5-minute intervals (for comparison with arterial catheter measurements)
- Central venous pressure
- Ventilation parameters (tidal volume, respiratory rate, PEEP, etCO2, FiO2 in inspired and expired gas mixture, and others).

6.7. Statistical Methods

6.7.1. Descriptive Methods

Descriptive methods are directly related to the distribution of statistical units by the values of their attributes, revealing their nature and internal structure. To apply descriptive methods correctly, observational units must be comparable and specific in time and place. Descriptive methods establish central tendencies, the degree of difference between individual observational units (patients), and the degree of deviation of the empirical distributions of observed units from standard distributions. Various methods are applied for each specific group of characteristics:

- Measures of central tendency such as mean, median, and mode
- Measures of dispersion such as standard deviation

- Measures of deviation from standard distributions such as skewness and kurtosis.

Graphical representation of empirical distribution is an essential part of descriptive statistical methodology. The following graphical representations are applicable: histograms, and frequency polygons. All the described elements were processed using SPSS v. 26.0.

6.7.2. Correlation Analysis

Correlation analysis is a statistical method that measures the strength and direction of the correlation between two or more phenomena. When developing a correlation model, it is essential to correctly define the independent variable X (factor) and the dependent variable Y (consequence). The main measure of the strength of the relationship is the correlation coefficient r, whose value is interpreted according to the scale presented below.

0	No relationship
0-0,3	Weak relationship
0,3-0,5	Moderate relationship
0,5-0,7	Significant relationship
0,7-0,9	Strong relationship
0,9-1	Very strong relationship
1	Perfect relationship

Table 1 Interpretation of the correlation coefficient r

When the correlation coefficient r has a positive value, it can be stated that there is a direct relationship between the phenomena. With a negative sign of the correlation coefficient r, it is claimed that the relationship is inverse. For the correct conduct of correlation analysis, the following steps need to be followed:

1. Determine the independent variables (factors) X and the dependent variable Y (consequence).
2. Select an appropriate correlation coefficient, according to the statistical scale to which the studied variables belong.
3. Evaluate the strength of the correlation relationship.
4. Assess the statistical significance of the obtained coefficient.
5. Interpret the results obtained. It is essential to evaluate whether the obtained correlation coefficient is statistically significant. In the context of using modern statistical and econometric software products, science allows for a decision to be made in an alternative way (without calculating an empirical value). The decision comes down to comparing the perceived standard level of significance (risk of error α) and the calculated threshold level of significance (Significance). This method is applied in the present study when testing for the statistical significance of the obtained correlation coefficient r. If the calculated significance level (Sig) based on sample data is less than the perceived standard level of significance (α), it is assumed that the obtained correlation coefficient is statistically significant and reliable. If the calculated significance level (Sig) is greater than the perceived standard level of significance (α), it is assumed that the obtained correlation coefficient is not statistically significant. Given the belonging of the variables to a specific statistical measurement scale, Spearman's correlation

coefficient, Pearson's correlation coefficient, and the non-parametric coefficient of contingency correlation have been applied.

IV. Results and Discussion

1. Demographic and clinical characteristics.

The study covers 73 clinical cases of patients who suffered from brain death at University Hospital "St. Marina" EAD, Varna, during the period 01.01.2014 - 31.12.2020. Due to its retrospective nature, Figure 4 presents the number of registered cases of brain death for this period and their trends during the specified period.

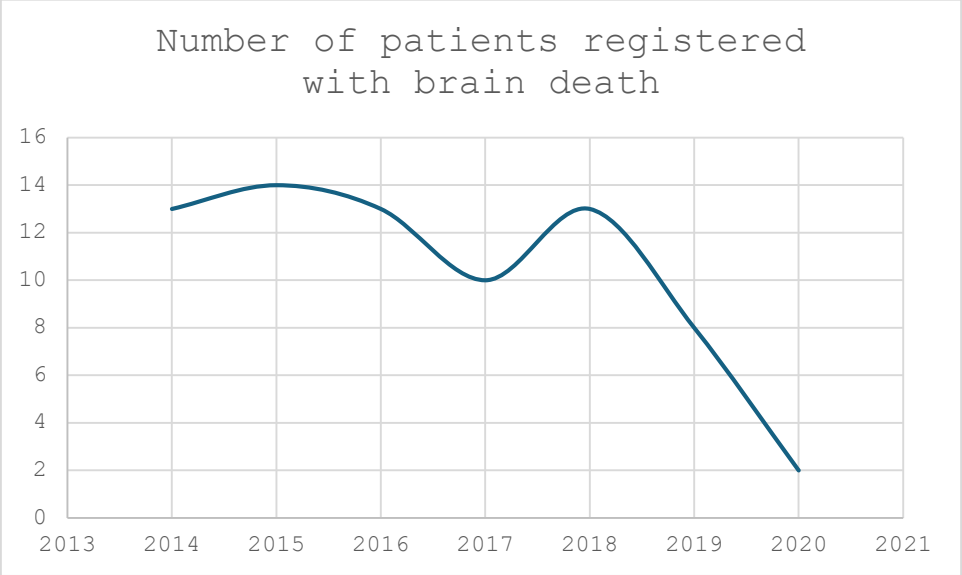


Figure 4 Number of registered cases of brain death in the period 2014-2020

During the initial years, the number of analyzed cases remains relatively constant with a slight decrease in 2017. However, from 2019, a significant decrease in patients diagnosed with brain death is observed, and a possible explanation for this could be the COVID-19 pandemic.

1.1. Gender.

Of all the patients included in the study, 35 (47.9%) are females, and 38 (52.1%) are males. This demonstrates a relatively even distribution concerning the "gender" attribute, as presented in Table 2 and graphically in Figure 5.

Gender

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Man	35	47,9	47,9	47,9
	Woman	38	52,1	52,1	100,0
	Total	73	100,0	100,0	

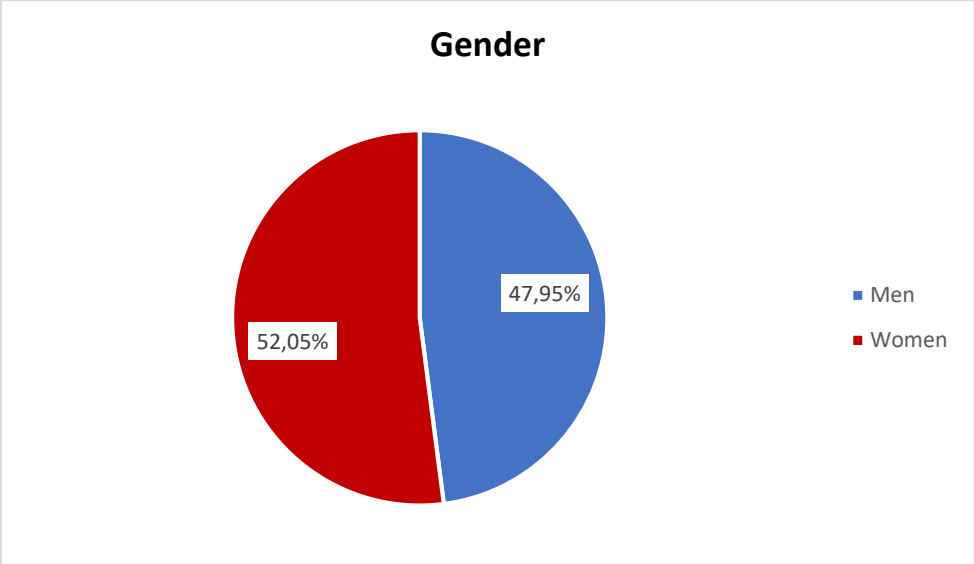


Figure 5 Distribution of patients by gender

1.2. Age

Age is another parameter we tracked. Table 3 presents the age characteristics of the sample in our study.

Statistics

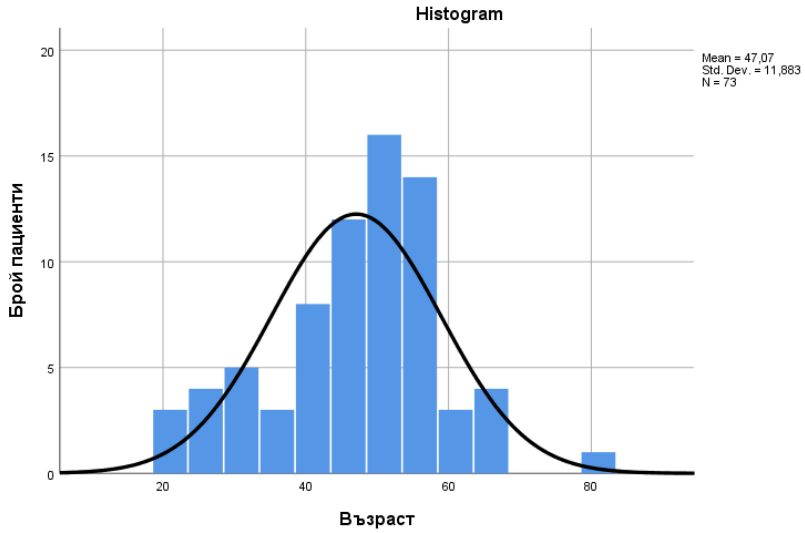
Age

N	Valid	73
	Missing	0
Mean		47,07
Median		49,00
Mode		47[a]
Std. Deviation		11,883
Skewness		-,163
Std. Error of Skewness		,281
Kurtosis		,435
Std. Error of Kurtosis		,555
Minimum		21
Maximum		83

Table 3 Distribution of patients by age

The average age of the patients included in the study is 47 years. The most common age among the patients is 47 years, occurring in 6 or 8.2% of all 73 patients. The variation in the "Age" attribute is approximately 12 years, with the youngest patient being 21 years old and the oldest being 83 years old,

respectively. The distribution of all 73 patients by the "Age" attribute exhibits moderate right-skewedness, as evident from the histogram below.



1.3. Etiology.

During the study, we considered the following data as possible causes leading to irreversible brain damage. Table 4 presents the distribution of patients according to the etiology of the process.

Etiology

		Frequency	Percent	Valid Percent	Cumulative Percent
Diagnosis		33	45,2	45,2	45,2
		20	27,4	27,4	72,6
		5	6,8	6,8	79,5
		1	1,4	1,4	80,8
		2	2,7	2,7	83,6
		1	1,4	1,4	84,9
		11	15,1	15,1	100,0
		73	100,0	100,0	

Table 4 Distribution of patients according to the etiology of the process

Among the 73 patients included in the study, the most common diagnoses that may lead to the onset of brain death are hemorrhagic stroke, subarachnoid hemorrhage, and ischemic stroke, occurring in 33 (45.2%), 20 (27.4%), and 11 (15.1%) patients, respectively. These results, demonstrating the association between cerebrovascular incidents and the occurrence of acute brain injury, are consistent with those reported by Issac et al. and the European Committee on Organ Transplantation (Issac et al., 2020; Guide to the quality and safety of organs for transplantation, 2022). Similarly to their findings, we also find a

low frequency of infectious or neoplastic processes as causes of brain death. Despite the fact that, according to the same authors, traumatic brain injury is another leading cause of brain death, it is noteworthy that only 2 (2.7%) patients in our study were diagnosed with it. The described results are presented graphically in Figure 7:

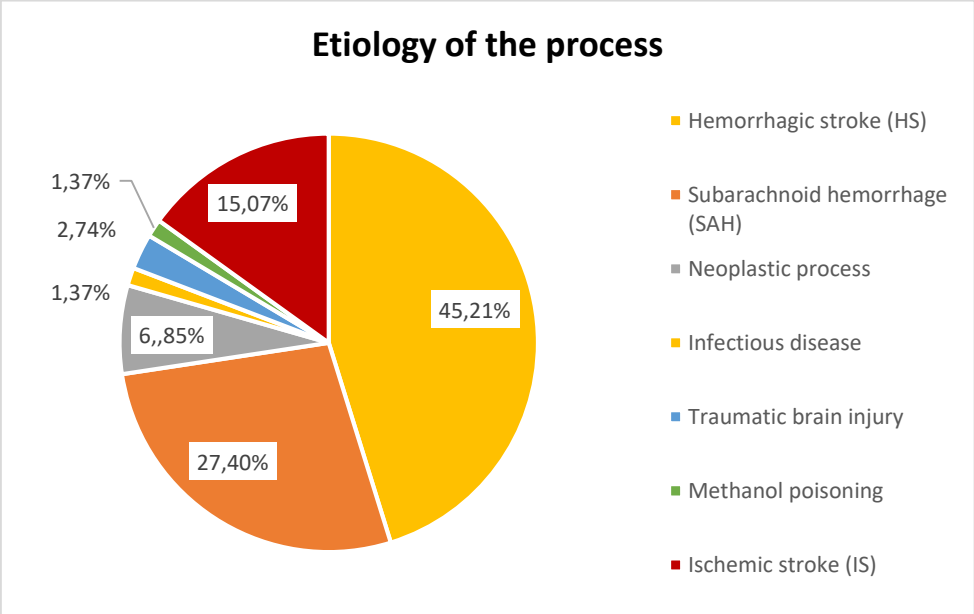


Figure 7: Distribution of patients according to the etiology of the process

, which are summarized in Table 5 and Figure 8. The diagnosis is based on clinical and paraclinical indicators – presence of polyuria (diuresis > 2ml/kg/h), urine specific gravity lower than 1.005g/ml, and

Diabetes insipidus

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	No	6	8,2	8,2	8,2
	Yes	67	91,8	91,8	100,0
	Total	73	100,0	100,0	

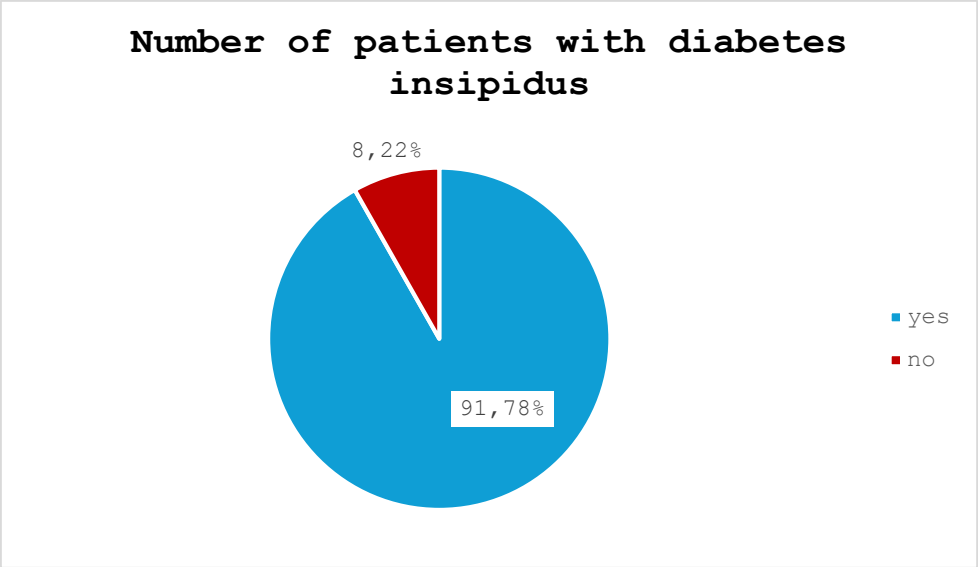


Figure 8 Number of patients with diabetes insipidus

Nearly 92% or 67 out of all 73 patients included in the study exhibit diabetes insipidus. According to literature data, due to the pathophysiological changes occurring in patients with brain death, diabetes insipidus develops in approximately 80% of cases (Issac et al., 2020). Other authors even report a higher percentage, up to 87%. The leading cause attributed to its occurrence is undetectably low levels of antidiuretic hormone in 75% of patients with brain death (Shemie et al., 2014).

2. Changes in plasma sodium concentration and their correction in the intensive care unit.

2.1. Changes in plasma sodium concentration.

A common deviation from normal plasma sodium concentration in patients with brain death is hypernatremia, defined as a plasma sodium concentration exceeding 145 mmol/L (Dictus et al., 2009; Noda et al., 2015). Such abnormal elevation of serum sodium levels is observed during the development of diabetes insipidus, which occurs in a high percentage of these patients (Marino et al., 2014). Hypernatremia may also result from excessive fluid replacement aimed at ensuring hemodynamic stability or hyperosmolar therapy to reduce intracranial pressure during the initial brain injury (Dictus et al., 2009; Yoshikawa et al., 2021). Regardless of the cause, the condition must be recognized and corrected promptly. In our study, we monitored the portion of patients who exhibited sodium levels exceeding the upper reference limit during the hospitalization of patients upon brain death registration, as well as at 6, 12, and 24 hours after brain death registration. We adopted the reference values for serum sodium within the range of 134–145 mmol/L (corresponding to normonatremia). All results below 134 mmol/L were interpreted as hyponatremia, and those exceeding 145 mmol/L as hypernatremia. Upon monitoring serum sodium levels during hospitalization, we found that in 68 (93.2%) of patients, there were no deviations from the reference limits. Only 5 (6.8%) of patients exhibited hypernatremia during this period. The ratio between patients with registered normonatremia and hypernatremia is presented in Figure 9.

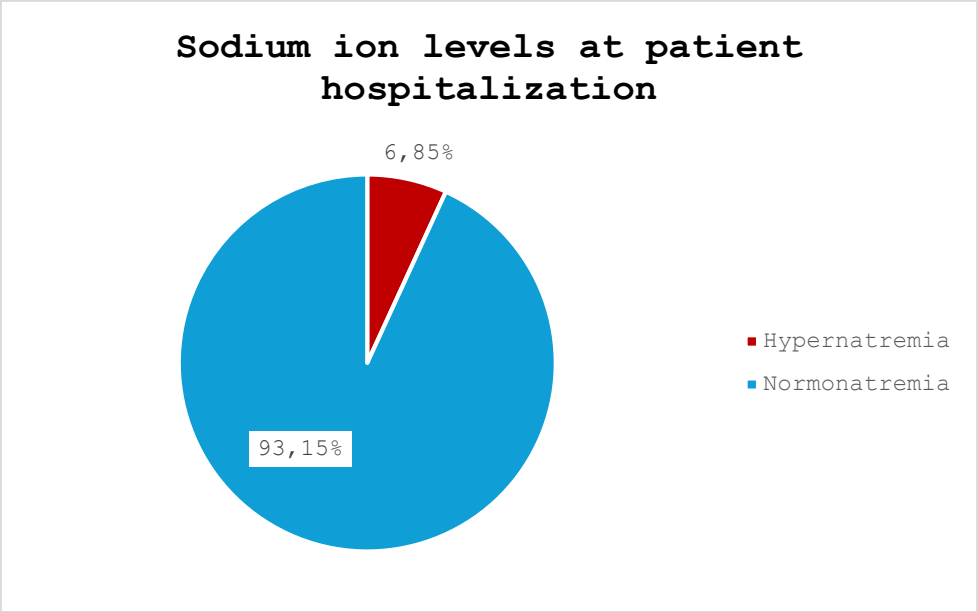


Figure 9 Sodium ion levels at patient hospitalization

Our opinion is that this deviation from normal sodium values at hospitalization cannot be attributed to the aforementioned causes of hypernatremia in patients with brain death since at this stage they did not have diabetes insipidus, and osmotic diuretics or hypertonic saline solutions were not administered. We attribute the abnormal values to the impaired consciousness of the patients and the inability to maintain fluid balance in their bodies through the sensation of thirst and fluid intake. A similar relationship between altered levels of consciousness and dysnatremia (more so for hypernatremia than for hyponatremia) is described by de la Hoz et al. in their study regarding critically ill patients. By examining serum sodium levels and assessing patient consciousness according to the Glasgow Coma Scale (GCS) upon admission to the hospital, they conclude that hypernatremia is unlikely to be iatrogenically induced. As a probable explanation for it, they suggest the inability to regulate fluid balance through the sensation of thirst and independent water intake due to consciousness disturbances (de la Hoz MAA et al., 2023). We also observe similar results when tracking the likelihood of a connection between states with consciousness disturbances and hypernatremia. In Tables 6 and 7, a tendency for such a connection is observed in the results of certain conditions. The calculated contingency coefficient of 0.306 indicates a moderate positive correlation between the two variables. The coefficient can be considered statistically reliable ($p = 0.0275 > \alpha = 0.05$), given that the calculated significance level /p/ is greater than the accepted 5% error risk.

Crosstab

Count

		Sodium at hospitalization		
		Hypernatremia	Normonatremia	Total
Diagnosis		3	30	33
		1	19	20
		0	5	5
		0	1	1
		1	1	2
		0	1	1
		0	11	11
Total		5	68	73

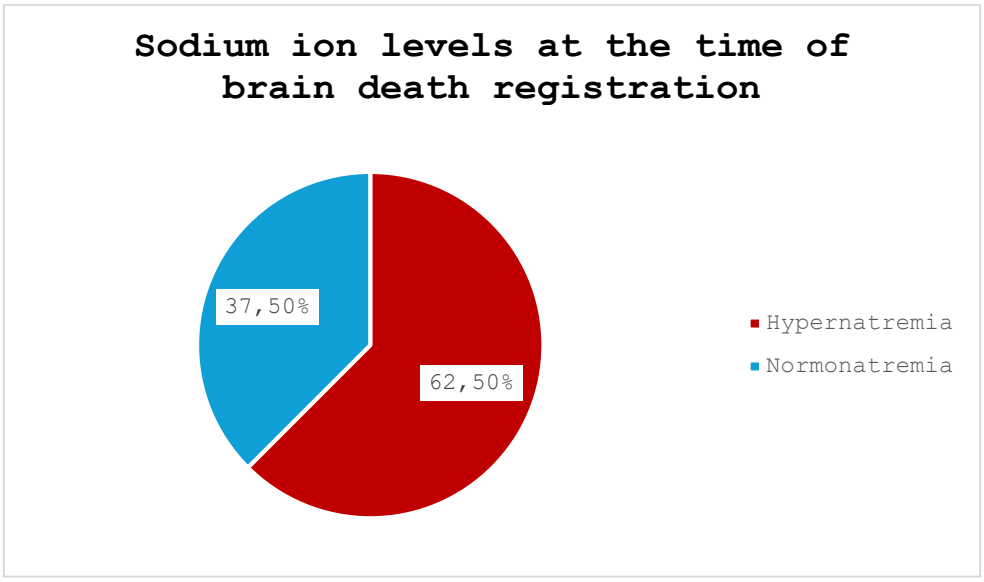
Table 6 Sodium ion values depending on the etiology of the process

Symmetric Measures

		Value	Approximate Significance
Nominal by Nominal	Contingency Coefficient	,306	,275
N of Valid Cases		73	

Table 7 Relationship between sodium ion values and etiology of the process

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid		45	61,6	62,5	62,5
		27	37,0	37,5	100,0
	Total	72	98,6	100,0	
Missing	System	1	1,4		
Total		73	100,0		



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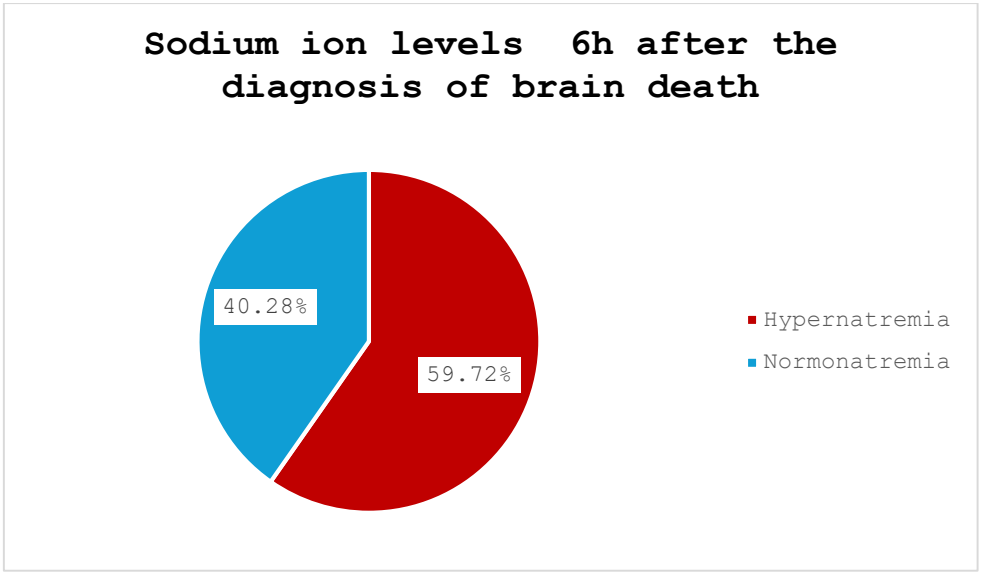
A likely explanation for the increase in the number of cases with registered hypernatremia could be the onset of diabetes insipidus. As previously mentioned, this diagnosis was made in nearly 92% of the patients included in the study.

When observing the serum sodium values over time, initially, there is a decrease in the number of patients with hypernatremia. Their number at the 6th hour from the diagnosis of brain death is 43 (59.72%) out of all 73 patients in the sample. With further monitoring of sodium values, a gradual increase in cases is observed: 49 (67.12%) at the 12th hour and 50 (68.49%) at the 24th hour. These changes are presented in Figures 11, 12, and 13.



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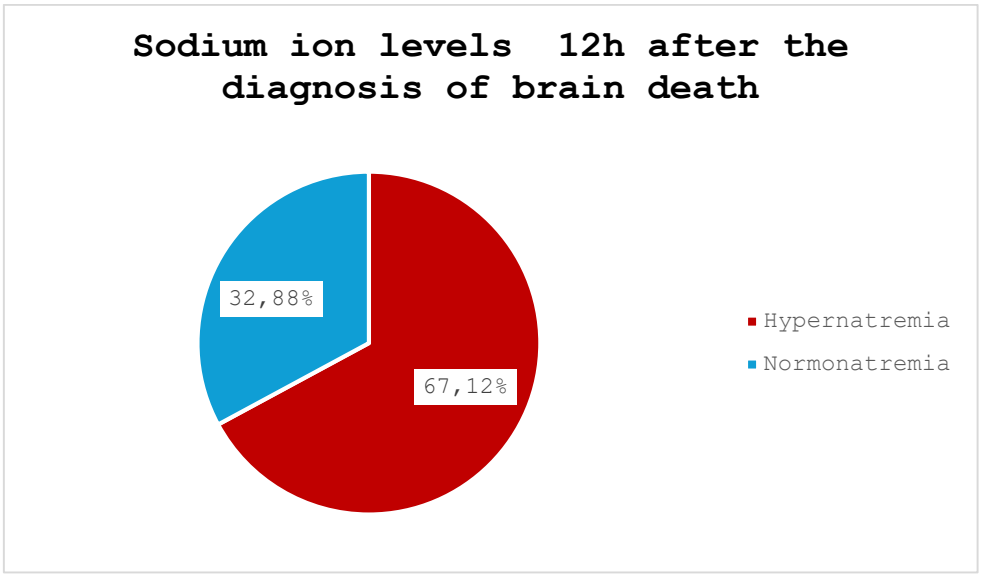

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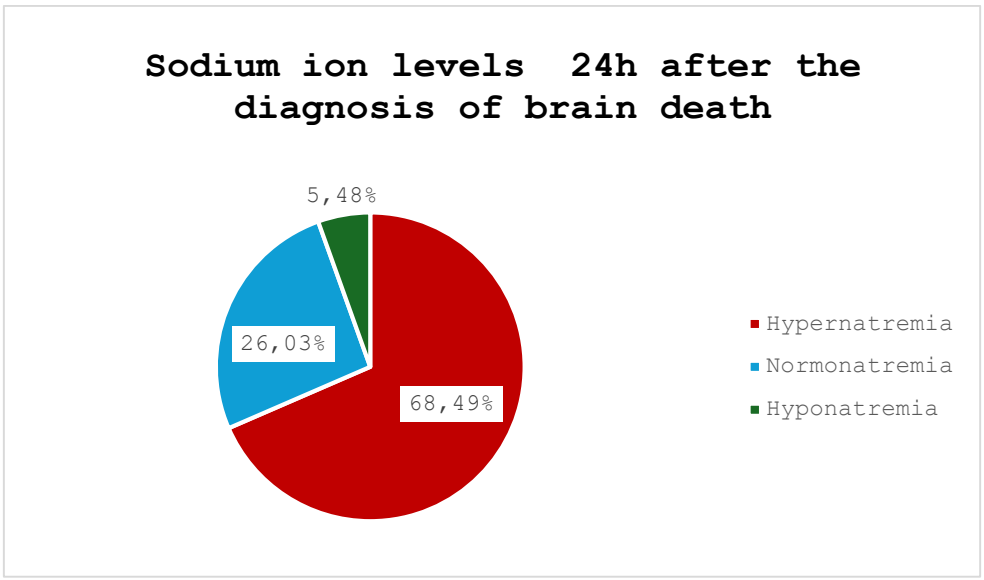

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The last figure is remarkable for the appearance of hyponatremia in 4 (5.48%) of the patients, which could be explained by excessive efforts to correct the preceding hypernatremia.

Table 10 presents the data tracking serum sodium values over hours in an aggregated form. The mean serum sodium values in the patient cohort were highest (152±14.4mmol/L) at the time of brain death diagnosis when the highest values were recorded during monitoring - 198 mmol/L. Guo et al. reported a rise in sodium values after 36.0 (28.5-52.3) hours, reaching peak values at 79.0 (54.0-126.0) hours (Guo et al., 2022). The lowest sodium values were measured at 24 hours after brain death diagnosis - 113 mmol/L. Our literature review did not uncover data on serum sodium changes over hours from other medical centers to compare with our experience.

Descriptives

	Na+ at hospitalization	Na+ at the time of brain death registration	Na+ 6h after the diagnosis of brain death	Na+ 12 after the diagnosis of brain death	Na+ 24 after the diagnosis of brain death
N	73	72	72	73	73
Missing	0	1	1	0	0
Mean	139	152	147	149	151
Median	139	152	148	148	152
Standard deviation	4.63	14.4	10.8	10.7	12.4
Minimum	128	125	124	121	113
Maximum	160	198	188	172	181

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2.2. Correction of Hypernatremia

As evident, hypernatremia in an organ donor with brain death can result from various factors. In our representative sample, cases were attributed to untimely control of diabetes insipidus, which develops in this patient group, and hyperosmolar therapy to combat increased intracranial pressure. Regardless of the cause, we recognize the importance of timely management to successfully proceed with the donation process. Kim et al. also note a more favorable prognosis with rapid correction (reduction by 1 mmol/L per hour), but recommend slower reduction of serum sodium levels in patients with long-standing or unknown hypernatremia (Kim et al., 2006). According to Totsuka et al., correction of hypernatremia to levels ≤ 155 mmol/L would yield the same success in grafts as those from donors who have never been hypernatremic (Totsuka et al., 1999). Shemie et al. suggest the ideal range for serum sodium to be ≥130 ≤150 mmol/L (Shemie et al., 2006).

Given the development of central diabetes insipidus in nearly 92% of the patients in the study, due to depletion of antidiuretic hormone, replacement therapy was initiated. According to literature, it can be carried out with vasopressin in cases of hemodynamic instability at a dose of 0.01-0.04 IU/min. Doses higher than this should be applied with increased caution due to the risk of splanchnic vasoconstriction (Kotloff et al., 2015; Shah et al., 2008). In the presence of significant hypernatremia (Na+ ≥145-150 mmol/L) without hypotension, treatment with desmopressin is initiated (Kotloff et al., 2015).

In our institution, Minirin (Desmopressin acetate) 0.2mg tablets were used, administered via nasogastric tube, as described in Table 10 and Figure 14.

Application of Minirin (Desmopressin acetate)

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	No	41	56,2	56,2	56,2
	Yes	32	43,8	43,8	100,0
	Total	73	100,0	100,0	

10 Application of Minirin (Desmopressin acetate)

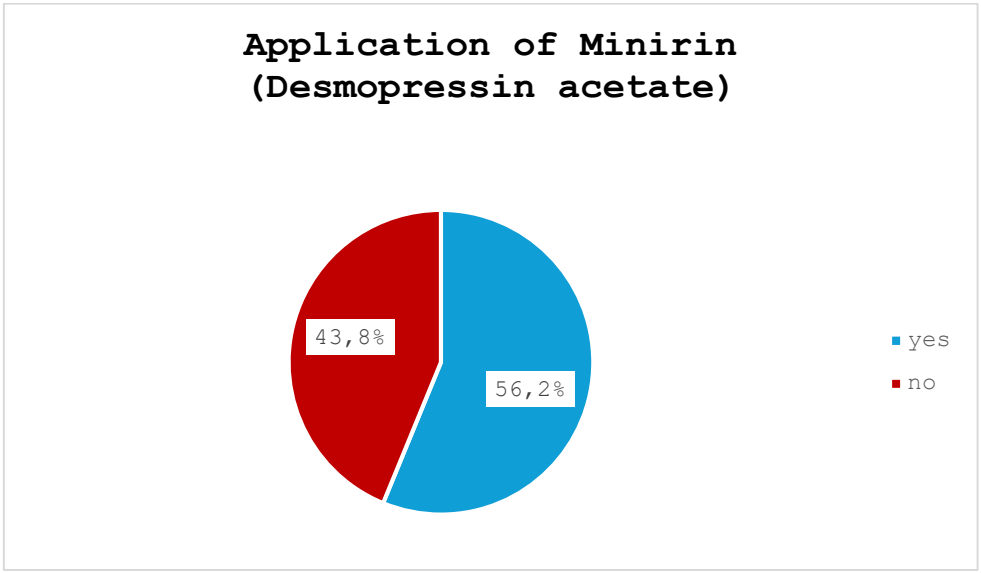

Figure 14: Application of Minirin (Desmopressin Acetate)"

According to our results, replacement therapy with desmopressin was used in only 56.2% (n=41) of the patients in the sample. The dose we managed to gather information about was 0.1mg when diuresis was >400ml/h, with strict control of urinary losses and monitoring of electrolytes.

Shemie et al. conclude in their study that in patients with brain death, desmopressin should be used intravenously at a dose of 0.5–10 μg every 6-8 hours. According to Kotloff et al., an initial dose of 1–4 μg of desmopressin should be applied, followed by additional doses of 1-2 μg every 6 hours, with the possibility of safely using higher doses. The lack of a vasopressor effect allows titration to regulate diuresis volume, urine osmolality, and normalize serum sodium levels.

Another indicator that was monitored was the application of pure water through the nasogastric tube during conditioning of the patients as organ donors to overcome hypernatremia in the context of hypovolemia. The obtained results, presented in Table 11, show that just over half (54.8%) of the patients in the representative sample received water to restore intravascular volume.

Pure water (ml/24h)

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	6 x 200	40	54,8	100,0	100,0
Missing	System	33	45,2		
Total		73	100,0		

Table 11: Application of Pure Water

It is important to note that the decision to use water for the purpose of restoring normovolemia in patients' bodies is made after calculating their water deficit using a formula. Similar recommendations are provided by the European Committee on Organ Transplantation, which suggests that in addition to water administration through the nasogastric tube, isotonic saline solution should also be used to restore intravascular volume. Only then do they recommend correcting the water deficit with a 5% glucose solution combined with insulin under strict control of blood sugar levels.

In the documentation required and obtained in connection with the present study, the total amount of electrolyte solutions included in the patients' infusion therapy within 24 hours was recorded. To analyze the results and compare them with those of other authors, we calculated the frequency of administration of the average amount of the respective solution applied within 24 hours. Table 12 and Figure 15 present the dose of 5% glucose solution administered within 24 hours. The highest percentage of patients received a dose of approximately 40ml/kg. The same dose is recommended by Boyadjieva et al. (Boyadjieva et al., 2019)

Sol. glucosae 5 % (dose/24hours)

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	6,2ml/kg	2	2,7	3,2	3,2
	12,5ml/kg	2	2,7	3,2	6,5
	18,75ml/kg	9	12,3	14,5	21,0
	25ml/kg	5	6,8	8,1	29,0
	31,25ml/kg	2	2,7	3,2	32,3
	37,5ml/kg	13	17,8	21,0	53,2
	43,75ml/kg	3	4,1	4,8	58,1
	50ml/kg	5	6,8	8,1	66,1
	56,25ml/kg	4	5,5	6,5	72,6
	62,5ml/kg	9	12,3	14,5	87,1
	68,75ml/kg	1	1,4	1,6	88,7
	75ml/kg	4	5,5	6,5	95,2
	81,25ml/kg	1	1,4	1,6	96,8
	87,5ml/kg	1	1,4	1,6	98,4
	118,75ml/kg	1	1,4	1,6	100,0
	Total	62	84,9	100,0	
Missing	System	11	15,1		
Total		73	100,0		

Table 12: Application of Sol. Glucosae 5%

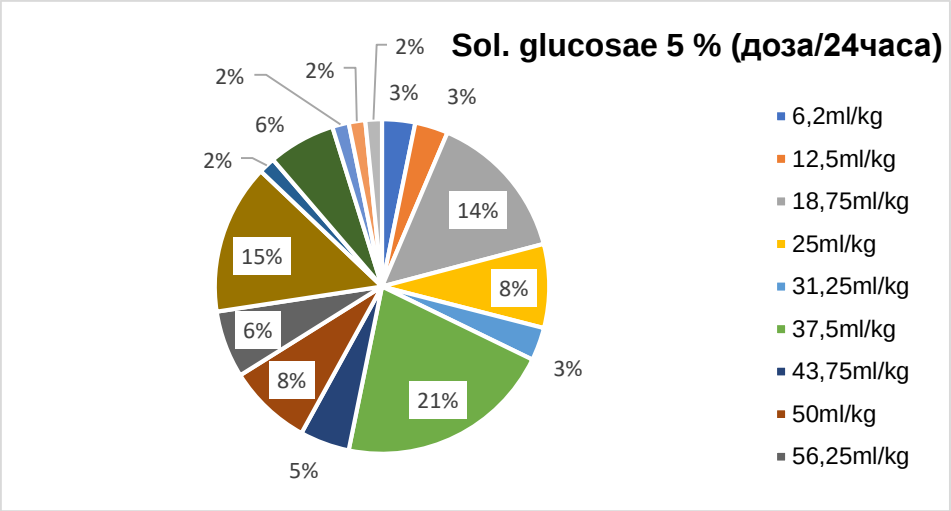

Figure 15: Application of Sol. Glucosae 5%

An impression from the obtained data is that in 15.1% (n=11) of patients, a 5% glucose solution was not applied. An explanation for this could be the application of another isotonic glucose solution or the use of another method to address hypernatremia in these patients.

From the available medical documentation, we found information that a 10% glucose solution was used in some patients. It was included as part of the infusion therapy for nearly 25% (n=18) of patients diagnosed with brain death. The collected data reflect the total amount of the solution applied within 24 hours, so we calculated the daily dose received by the patients in the sample.

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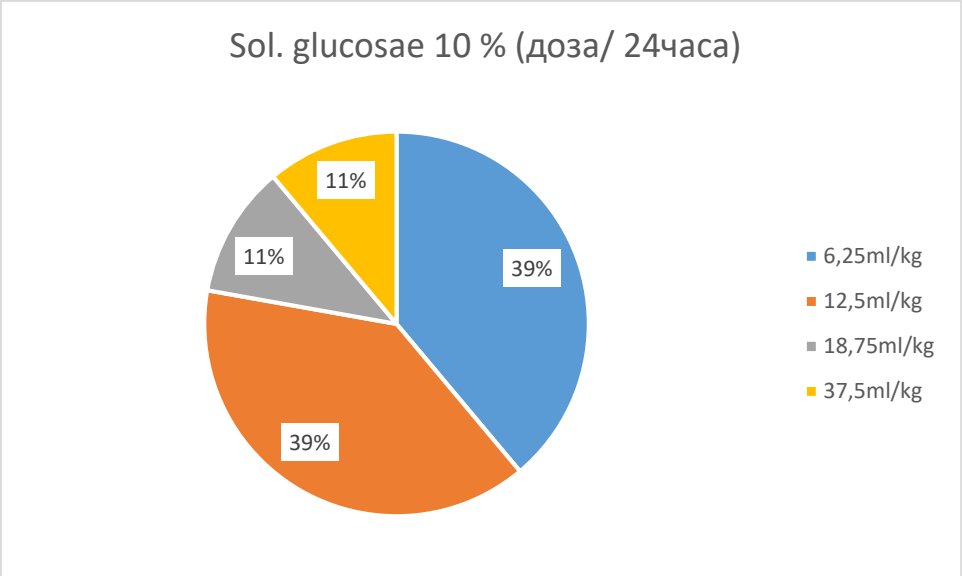


Figure 16: Application of Sol. Glucosae 10%

The results in Table 13 clearly indicate that the higher percentage of isotonic glucose solution was applied in nearly 80% of patients at a dose of 6-12ml/kg. Higher dosages were used much less frequently in our institution. However, literature provides information on its use in doses up to 40ml/kg (Boiadzhieva et al., 2019).

"In summary, glucose-containing electrolyte solutions were included in the therapy of almost 90% of patients in the study. This distribution is presented in Table 14 and graphically depicted in Figure 17.

Application of glucose-containing electrolyte solutions

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	No	8	11,0	11,0	11,0
	Yes	65	89,0	89,0	100,0
	Total	73	100,0	100,0	

Table 14 Application of glucose-containing electrolyte solutions

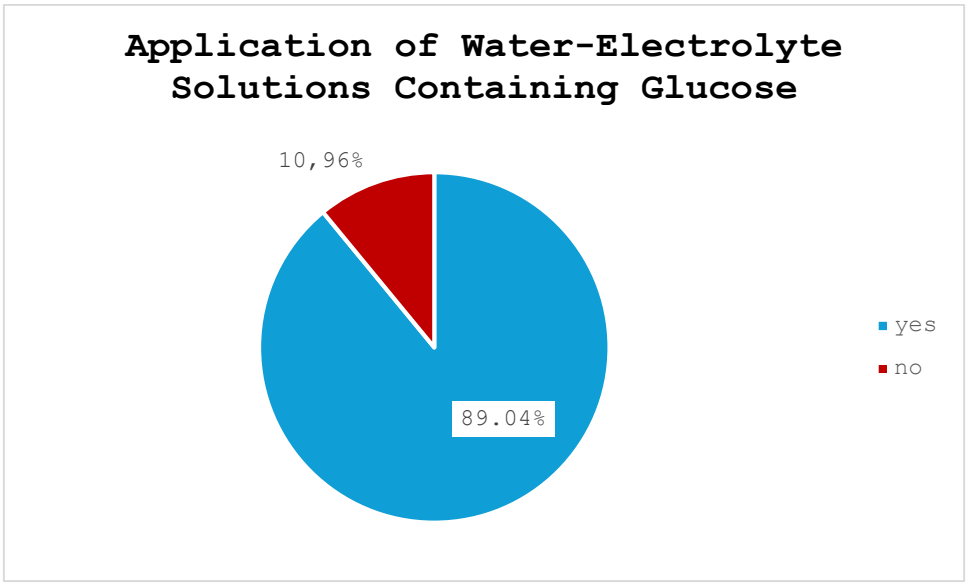
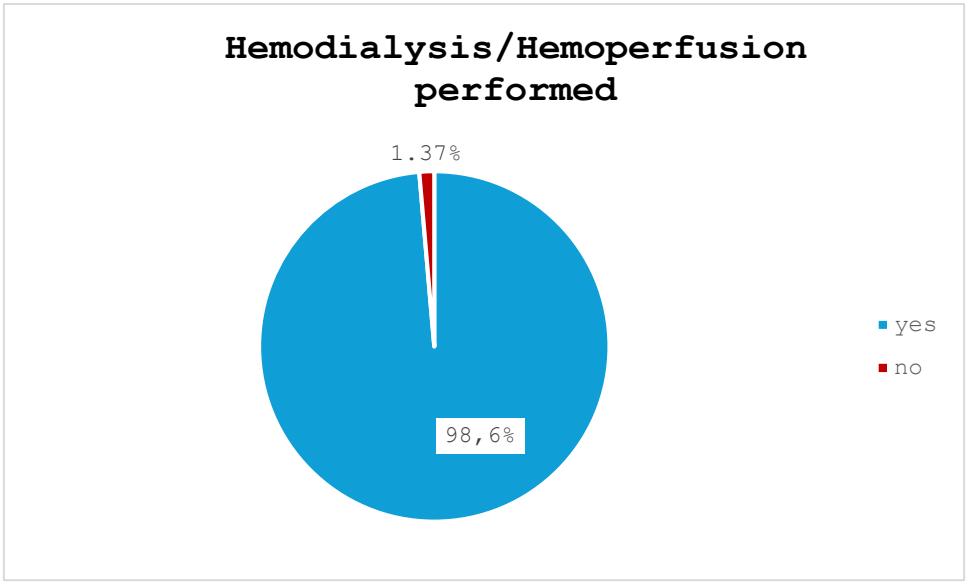


Figure 17 Application of glucose-containing electrolyte solutions

We note that along with the use of high-glucose solutions, strict monitoring of blood sugar levels was conducted for these patients.

The European Committee on Organ Transplantation recommends that the use of glucose-containing electrolyte solutions be preceded by the administration of Furosemide in cases of hypernatremia without water loss. As an alternative option in such situations, they consider the implementation of hemodialysis or hemoperfusion (Guide to the quality and safety of organs for transplantation, 2022).

In the representative sample of patients included in the study, hemodialysis was performed in only one case (1.37%). Considering the fact that initially, this patient was hospitalized in the Nephrology Clinic at our institution, we believe that the reason for the procedure was related to renal impairment that occurred before the onset of brain death. No data on the use of extracorporeal blood purification methods were found in the medical records of the remaining patients. The data is presented in Figure 18:



3. Changes in Plasma Chloride Ion Concentration and Its Correction in the Intensive Care Unit

3.1. Changes in Plasma Chloride Ion Concentration

Another parameter we monitored during our study was the plasma chloride ion concentration. An increase in their values above the upper reference limit, combined with the development of metabolic acidosis, can be observed in patients with elevated intracranial pressure as a result of aggressive use of hypertonic saline solutions (Mason et al., 2023; Rangel-Castillo et al., 2008; Raslan et al., 2007; Schizodimos et al., 2020; Susanto et al., 2022). Another cause of hyperchloremia in organ donors with brain death, as noted by Uchyltilova et al., is the frequent use of 0.9% saline and electrolyte imbalances associated with the development of diabetes insipidus. In their retrospective study involving 213 donor situations, they describe that 127 of them had hyperchloremia (Uchyltilova et al., 2017). Kieslichova et al. also describe the high incidence of hyperchloremia in patients with brain death – 39 out of the 52 included in their study met this criterion (Kieslichova et al., 2015). Similar factors are highlighted by Sharma et al. in their work, adding additional factors such as gastrointestinal and renal causes (Sharma et al., 2023).

For the purposes of our study, we accepted reference values for serum chloride in the range of 99-109 mmol/L, corresponding to normochloremia. All values below this lower limit were interpreted as hypochloremia, and those exceeding the upper limit were interpreted as hyperchloremia. These were monitored during patient hospitalization, upon registering brain death, as well as at 6, 12, and 24 hours after registering brain death.

After analyzing the collected information from the patients' medical documentation, we found that more than half of the patients in the study (68.5%) had normal serum chloride values during their hospitalization. Seventeen patients had values below 99 mmol/L, and only six were registered with hyperchloremia.

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		Frequency	Percent	Valid Percent	Cumulative Percent
Valid		50	68,5	68,5	68,5
		17	23,3	23,3	91,8
		6	8,2	8,2	100,0
	Total	73	100,0	100,0	

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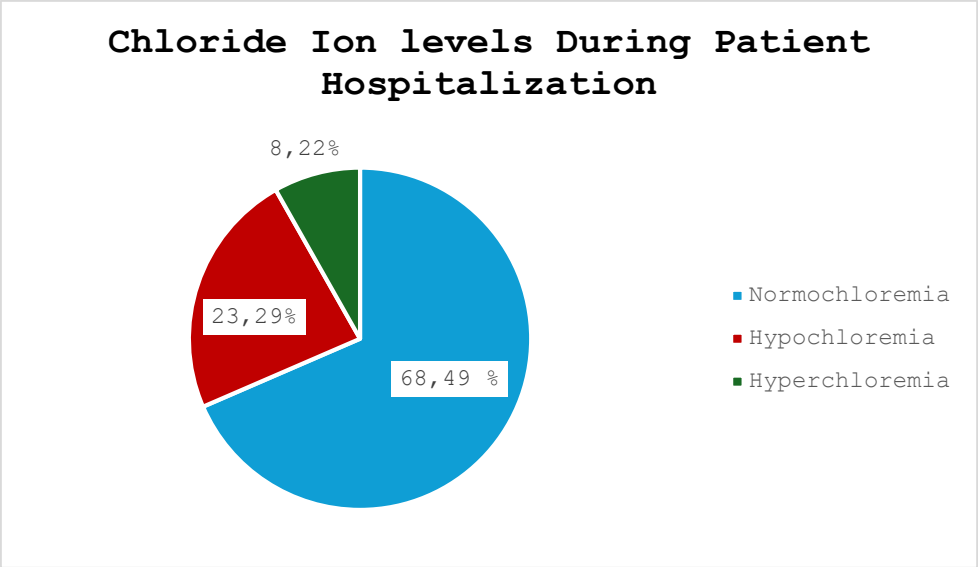

Figure 19. Chloride Ion levels During Patient Hospitalization

In our efforts to investigate the relationship between serum chloride values and the admission diagnosis, we found a significant direct correlation between the two variables, as indicated by the calculated contingency coefficient of 0.576. This coefficient can be considered statistically reliable ($p = 0.000 < \alpha = 0.05$), given that the calculated significance level (p) is less than the accepted risk of error of 5%.

Crosstab

Count

		Clorine at hospitalization			
		Normochloremmia	Hypochloremia	Hyperchloremia	Total
Diagnosis		20	11	2	33
		16	3	1	20
		2	2	1	5
		1	0	0	1
		0	0	2	2
		0	1	0	1
		11	0	0	11
Total		50	17	6	73

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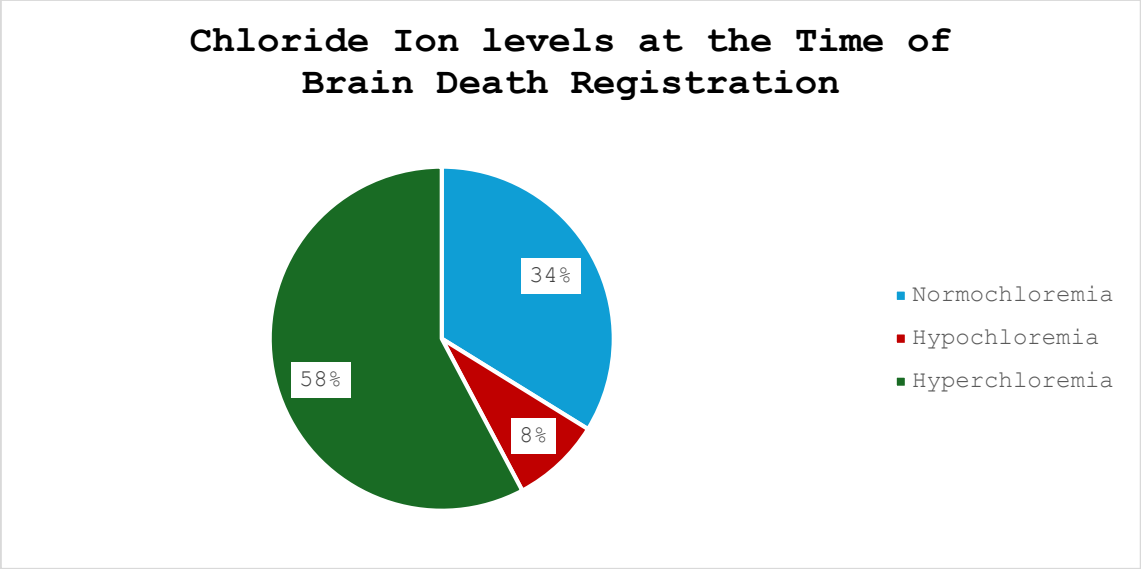
Symmetric Measures

		Value	Approximate Significance
Nominal by Nominal	Contingency Coefficient	,576	,000
N of Valid Cases		73	

Table 17. Relationship Between Chloride Ion levels and the Etiology of the Process

In tracking chloride values at the diagnosis of brain death, a significant increase in the number of patients with hyperchloremia is observed at the expense of those who were previously normochloremic and hypochloremic. High chloride values are observed in more than half of the patients—56.2% of the entire sample. For 2 patients (2.7%), no results for this period were found in the medical documentation provided for the purposes of the study. The results are shown in Figure 20:



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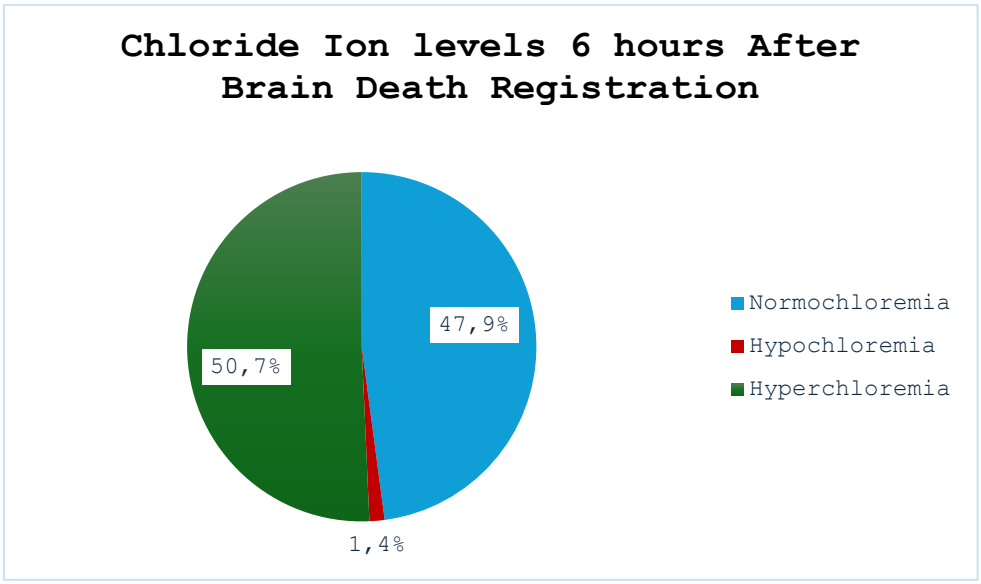
A possible explanation for the increase in serum chloride is preceding respiratory failure or inappropriate mechanical ventilation settings, leading to the accumulation of acidic products. This can be corrected by conducting artificial pulmonary ventilation with a tendency for hyperventilation of the patients (Sharma et al., 2023). Another cause could be untimely or poor control of diabetes insipidus, which was registered in a large part of the patients in our study.

Following the significant increase in the number of patients with hyperchloremia at the registration of brain death, a slight decrease in their number is observed in the subsequent hours (up to the 6th hour), down to 37 patients (50.7%). This decline is followed by a new rise in the next reporting period (up to the 12th hour) to 53 patients (72.6%). At the 24th hour after the diagnosis of brain death, a gradual decrease is observed in those with elevated serum chloride values, encompassing more than half of the patients in the study, or 60.3%. The trends in deviations from normal chloride values are presented in the figures below:



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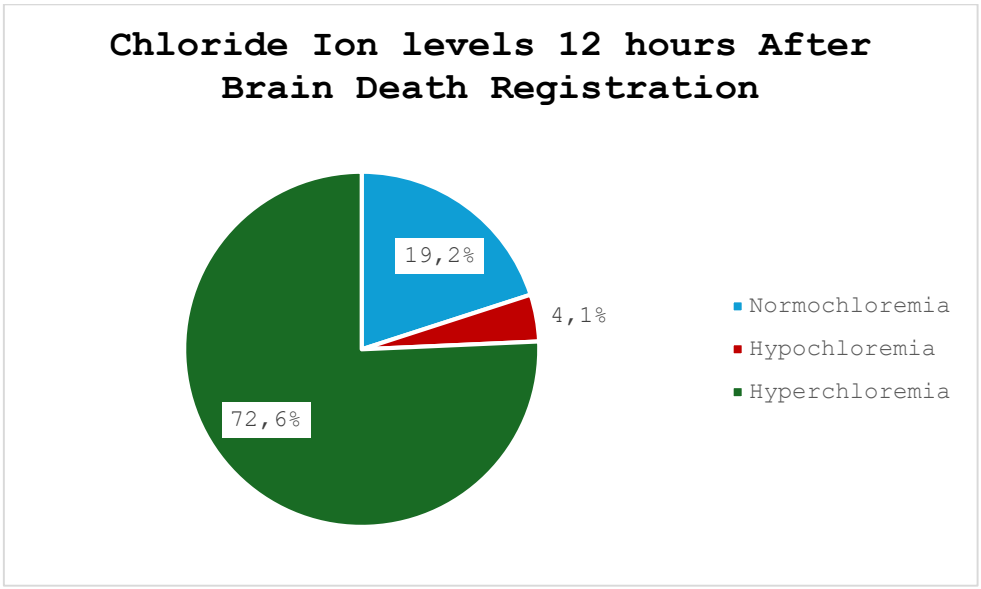

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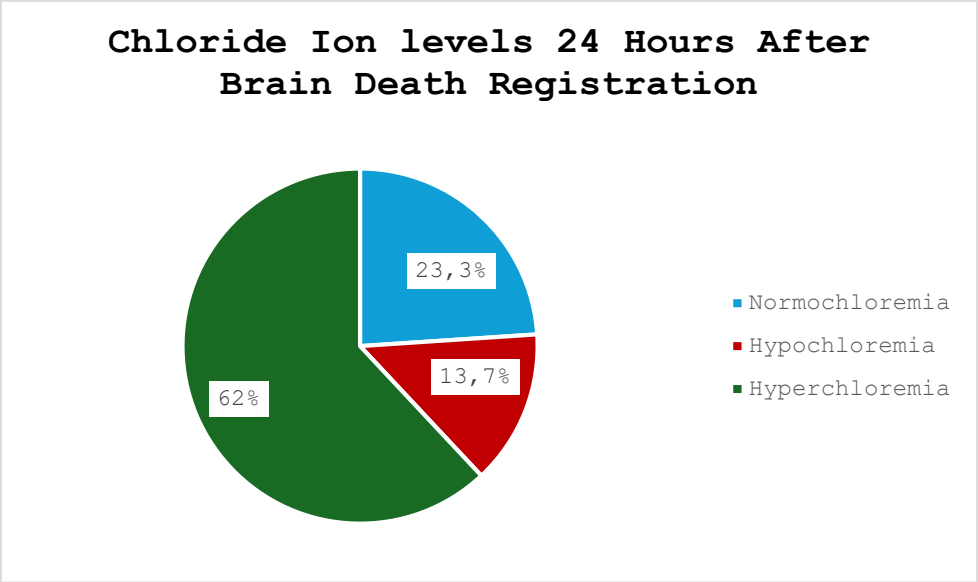

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Apart from the increase in the number of patients with rising chloride values, there is also a noticeable increase in the number of patients with values below the lower limit. These fluctuations in chloride values could be related to the efforts of medical teams involved in donor conditioning to correct deviations in water-electrolyte balance.

As previously mentioned, aggressive use of hypertonic saline solutions to combat elevated intracranial pressure can lead not only to hypernatremia but also to the development of hyperchloremic metabolic acidosis (Mason et al., 2023; Rangel-Castillo et al., 2008; Raslan et al., 2007; Schizodimos et al., 2020; Susanto et al., 2022). However, upon analyzing the data from the medical documentation, we did not find any patients who had been administered such preparations. This directed our attention to seeking other explanations for the observed changes.

Sharma et al. highlight the possibility of blood overload with chloride ions resulting from the administration of large amounts of 0.9% sodium chloride solution (Sharma et al., 2023). Table 18 presents the daily dose of 0.9% sodium chloride solution used in the patients included in our study.

Table 18. Application of 0.9% Sodium Chloride Solution

The crystalloid mentioned in the table was used as part of the infusion therapy in only 11% (n=8) of the patients included in the present study. To determine the dose, Tonog et al. suggest using the "100-50-25" or "4-2-1" formulas (Tonog et al., 2024). Following this principle, we calculated that the daily dose for an 80-kilogram patient is 37.5 ml/kg, which is significantly higher than the amount administered to the patients in the study. This excludes overload with 0.9% physiological saline solution as the cause of hyperchloremic metabolic acidosis.

In conclusion, the probable reason for deviations from normal chloride ion values is the onset of diabetes insipidus. The summarized data from the tracked serum chloride values within the reporting periods are presented in Table 19. The mean serum chloride values were highest (114±12.5 mmol/L and 114±7.52 mmol/L) at the registration of brain death and at the 12th hour thereafter. Similar mean values are reported by other medical centers—113.6±2.9 mmol/L (Uchytilova et al., 2017). Supporting these data are those reported by Kieslichova et al., who report measured mean chloride ion values in patients with brain death of 117.92±10.82 mmol/L (Kieslichova et al., 2015). Our team recorded the highest values at the diagnosis of brain death, specifically 153 mmol/L, considering this period and the 12th hour thereafter as peak periods. Reviewing Bulgarian and international literature, we failed to find data regarding this criterion for comparison.

	at the time of brain death registration	**6h after the diagnosis of brain death**	**Cl- 12ч after the diagnosis of brain death**	**Cl- 24ч after the diagnosis of brain death**

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In the medical documentation we collected for the purposes of this study, there was no information found regarding the policy for mechanical ventilation of patients and the implementation of hyperventilation. Therefore, there is no way to analyze it as a method for correcting hyperchloremic metabolic acidosis.

The treatment of the condition begins with identifying the underlying cause, which can be well influenced by adding bicarbonates to physiological saline until the underlying pathology is corrected. Sharma et al. recommend the use of bicarbonates at a dose of 5-15 mEq/kg/day, potassium replacement, and the inclusion of vitamin D (Sharma et al., 2023). Smilov et al. suggest the application of bicarbonates at close doses (10-25 mmol/kg/day) in combination with potassium compounds (Smilov et al., 2007).

We found that bicarbonates were used among a small portion of the patients in our study. The results are shown in the following table:

Bicarbonates

No				
Ye				
Ye				
Ye				
Ye				

Bicarbonates were administered to 7 out of the total 73 patients (9.6%). In two cases, these agents were applied during cardio-pulmonary resuscitation.

Regarding the application of vitamin D, none of the patients conditioned as organ donors with brain death received such a preparation.

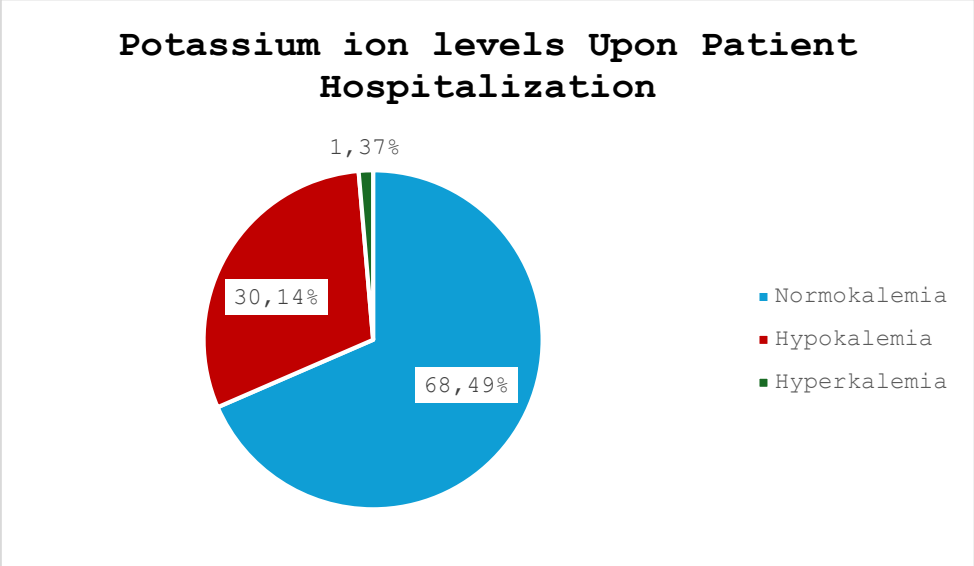
Hyperchloremic metabolic acidosis leads to hypovolemia and hypokalemia. Tracking the latter in the representative sample, as well as managing it, will be discussed in the following points of the exposition.

The next object in our study is the plasma concentration of potassium cations. Dominguez-Roldan, J M et al. report that hypokalemia is observed in 70% of patients with brain death. The reasons for this, according to Srivastava, Vikas et al., may be associated with the onset of diabetes insipidus, osmotic diuresis, high blood glucose levels, insulin intake, or inadequate potassium intake. Another reason, for

which there is data in the literature, is the development of respiratory alkalosis. There is also mention of a link between the presence of hypomagnesemia and low serum levels of K+.

To check for deviations from normal potassium values in patients included in the present study, we tracked the results of their examination during hospitalization, upon diagnosis of brain death, as well as at 6, 12, and 24 hours after diagnosis. For reference values, we adopted those within the range of 3.5-5.5 mmol/L, considering them as normokalemia. All results exceeding the upper limit were defined as hyperkalemia. Values lower than 3.5 mmol/L were divided into two groups - patients with hypokalemia (with measured values between 2.5 and 3.5 mmol/L) and patients with severe hypokalemia (with measured values below 2.5 mmol/L).

From Figure 24, it is clear that almost 70% of the patients, the subject of our study, had normal potassium ion values during hospitalization. The unexpectedly high percentage (around 30%) of cases of hypokalemia is striking. Probably an explanation for this is inadequate potassium intake, as mentioned by Srivastava, Vikas et al.



ion levels Upon Patient Hospitalization

As confirmation of this hypothesis regarding the etiology of hypokalemia, the frequency of its occurrence among the various admission diagnoses of patients can be considered, taking into account its frequency in acute incidents leading to brain damage. The results are presented in the following tables:

Potassium at hospitalization		
Normokalemia	Hypokalemia	Hyperkalemia

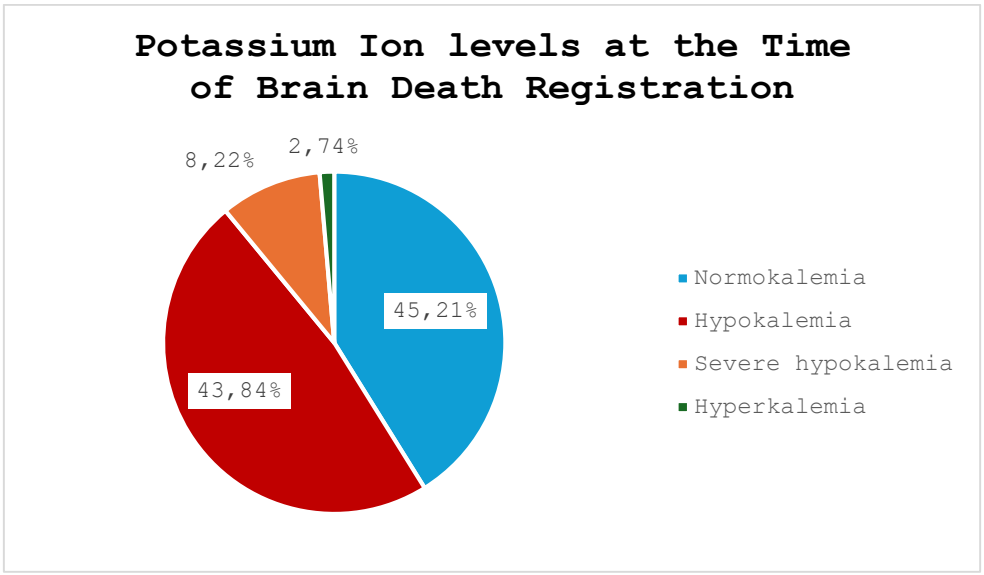
Diagnosis					

Table 21: Potassium ion levels Based on the Etiology of the Process

Table 22: Relationship Between Potassium ion levels and the Etiology of the Process

The calculated contingency coefficient of 0.345 indicates the presence of a moderate positive correlation between the two variables. However, the coefficient cannot be considered statistically reliable ($p=0.627>\alpha=0.05$), given that the calculated significance level /p/ is greater than the accepted risk of error of 5%.

The relatively low percentage of patients with hypokalemia during hospitalization increases to 52% when tracking serum potassium values after the diagnosis of brain death has been established, reaching almost double values (57.5%) at the 6th hour after diagnosis. The change is depicted in Figure 25 and Figure 26.



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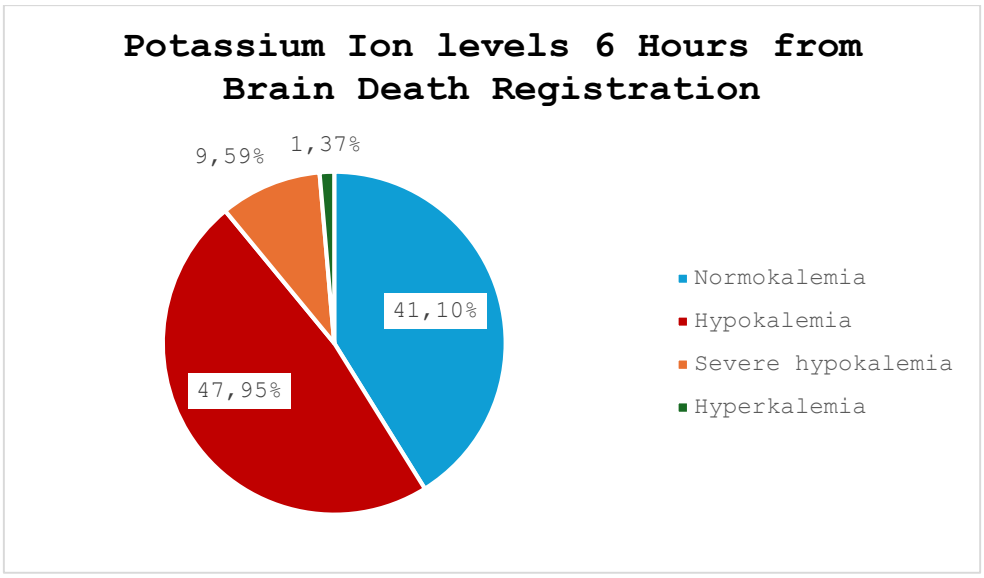


Figure 26: Potassium ion levels 6 Hours from Brain Death Registration

It should be noted that the percentages described above include not only those with hypokalemia but also those with severe hypokalemia (a condition not observed in any of the patients during hospitalization).

A probable explanation for the depletion of potassium cations can primarily be found in the development of diabetes insipidus in a large portion of the patients – as previously mentioned, it was recorded in 91.8% (n=67) of them. Dominguez-Roldan, J M et al. report similar findings, stating that 85% of the patients in their sample developed diabetes insipidus. The same assertion is supported by several other studies by various authors.

Another possible reason could be the high levels of blood glucose and/or insulin administration. Several authors have written about this in their reports. The number of patients who experienced hyperglycemia with or without insulin administration is presented in Table 23.

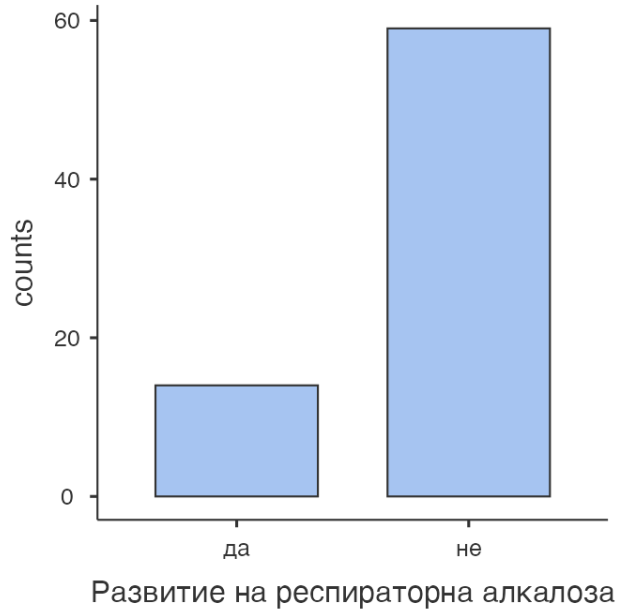
Period of hyperglycemia

Period of hyperglycemia		
Yes, without application of insulin	15.1 %	15.1 %
Yes, with application of insulin	32.9 %	47.9 %
He	52.1 %	100.0 %

Table 23: Periods of Hyperglycemia

The data from the conducted analysis indicate that episodes of elevated blood glucose levels were observed in almost half of the cases (47.9%), with insulin administration being necessary for the correction of hyperglycemia in nearly 33% of them. As described earlier, these results could also be associated with the observed hypokalemia.

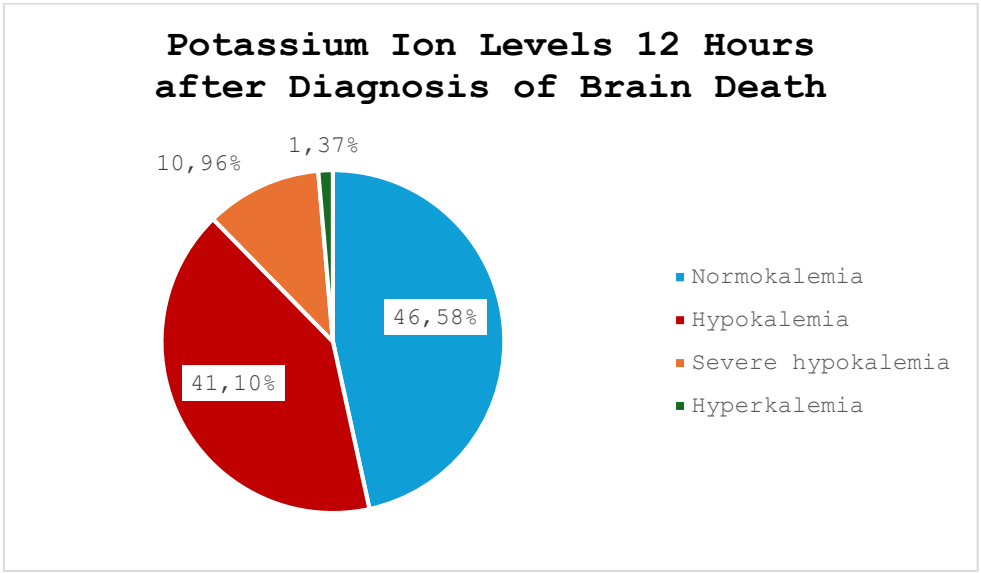
Another assumption for the occurrence of hypokalemia in patients diagnosed with brain death is highlighted by Powner, D J et al. and Power, B M, and P V Van Heerden, who emphasize the influence of respiratory alkalosis resulting from hyperventilation aimed at reducing intracranial pressure.

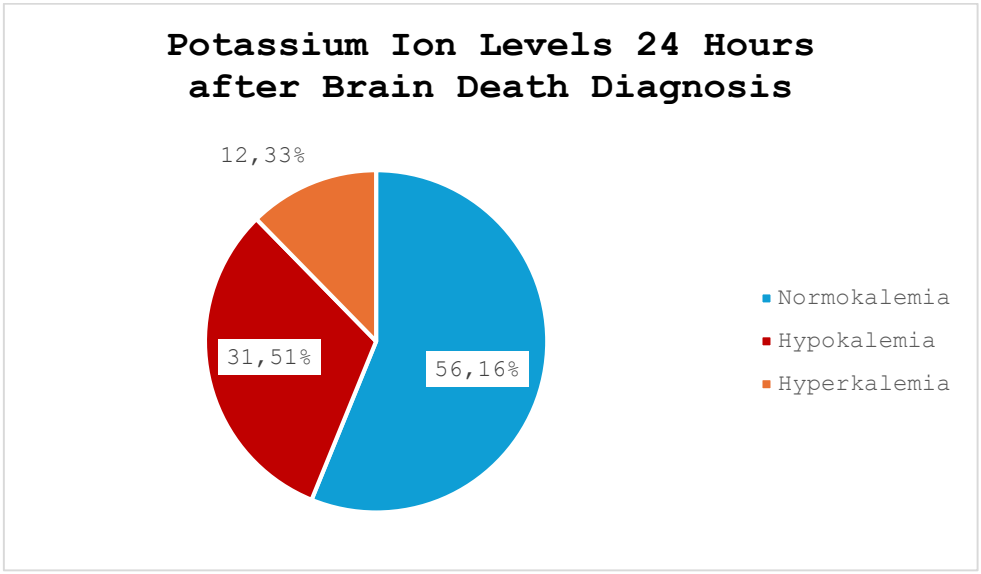


It is observed that a similar change in the acid-base balance was observed in almost 20% (n=14) of the patients in the sample.

According to Reynolds, Joanne L et al., hypokalemia may result from hypomagnesemia (Reynolds et al., 2004). However, such hypomagnesemia was observed in only about 10 to 19% of the patients included in our study.

Tracking serum potassium levels at 12 and 24 hours after diagnosis reveals a gradual decrease in the number of patients with hypokalemia, which we attribute to the effect of ongoing treatment to correct the electrolyte imbalance.





Figures 28 and 29 demonstrate a gradual increase in the number of cases with normal serum potassium levels, at the expense of both those with mild and those with severe hypokalemia.

Table 24 presents an overview of the potassium ion values depending on the stage of their examination. The lowest mean value (3.48 ± 0.816 mmol/L) was recorded at 6 hours after the diagnosis of brain death, and the lowest values (1.3 mmol/L) were observed at the time of diagnosis of brain death and 6 hours later.

	K+ at patient hospitalization	**K+ at the time of brain death registration**	**K+ 6 after the diagnosis of brain death**	**K+ 12 after the diagnosis of brain death**	**K+ 24 after the diagnosis of brain death**

Table 24: Potassium Ion Levels during Different Follow-up Periods

We were unable to find information on this criterion in the available sources to compare the findings.

4.2. Correction of Hypokalemia

Correction of hypokalemia in our institution is achieved through intravenous administration of potassium chloride (KCl), which is available as a concentrated solution (2 mmol/ml) in 10 ml ampoules. It is administered as an infusion, with preference given to using a large central vein due to its irritating properties on the venous wall. Table 25 shows that replacement therapy was conducted in 75.3% of all patients included in the study. In some cases, it was administered as a continuous infusion at various doses, while in others, it was added to their infusion therapy. The results indicate that the majority of patients received a dose between 3.2-4 mmol/h.

A n		
A n		
y e	1.4 %	1.4 %
y e	11.0 %	12.3 %
yes, 2x1 амп	4.1 %	16.4 %
y e	16.4 %	32.9 %
yes, 3x1 амп	5.5 %	38.4 %
y e	31.5 %	69.9 %
y e	5.5 %	75.3 %
No	24.7 %	100.0 %

Table 25: Potassium Chloride (KCl) Application

5. Changes in Plasma Calcium Cation Concentrations and Their Correction in the Intensive Care Unit.

5.1. Changes in Plasma Calcium Cation Concentrations.

According to literature data, hypocalcemia occurs in 18% of hospitalized patients and 85% of those in the intensive care unit (Busl et al., 2021). Similar results are reported by Egi, Moritoki et al., describing that 88% of 7024 intensive care patients included in their study develop at least one episode of mild ionized hypocalcemia and 3.3% experience at least one episode of severe ionized hypocalcemia (Cywinski et al., 2008). Causes include alkalosis, hemotransfusion, fat embolism, administration of aminoglycosides or heparin, hypomagnesemia, pancreatitis, renal failure, and sepsis (Marino et al., 2014). In cases of brain death, developing diabetes insipidus may also contribute to hypocalcemia (Piriova et al., 2006; Busl et al., 2021; Cohn et al., 2000; McKee et al., 2005).

To determine if changes in calcium ion concentrations are observed similar to other electrolytes, we tracked their concentrations upon patient hospitalization, brain death diagnosis, and at the 6th, 12th, and 24th hours post-diagnosis. For the purposes of this study, we used laboratory-recorded values of ionized calcium. We defined the boundaries corresponding to normocalcemia as 1.15-1.32 mmol/L. Hypocalcemia was defined as ionized calcium values between 0.9-1.14 mmol/L, and those below 0.8 mmol/L as severe hypocalcemia. All results exceeding 1.32 mmol/L were categorized as hypercalcemia.

Similar to information found in the available literature, nearly half of the patients in our sample exhibited decreased calcium concentrations. Figure 30 shows that hypocalcemia was observed in 46.58% (n=34) of the patients, with 1.37% (n=1) experiencing severe hypocalcemia.

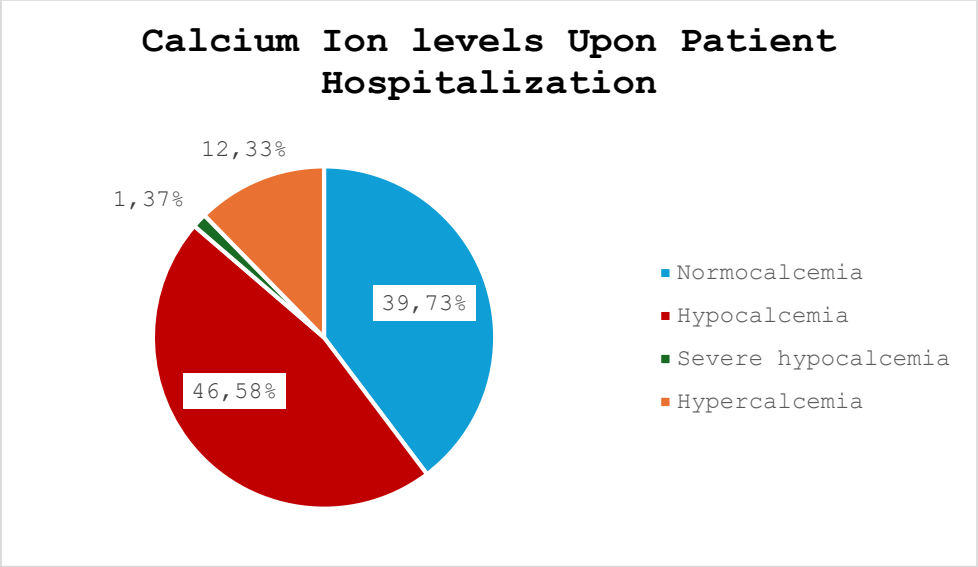


Figure 30: Calcium Ion levels Upon Patient Hospitalization

We also examined the relationship between the patient's admission diagnosis and changes in ionized calcium values. The results are presented in the following tables:

		Calcium at hospitalization				
		Hypocalcamia	Normocalcemia	Serious hypocalcemia	Hypercalcemia	
Dianosis						

Table 26: Calcium Ion Levels Depending on the Etiology of the Process

The calculated contingency coefficient of 0.397 indicates a moderate positive correlation between the two variables. However, the coefficient cannot be considered statistically reliable (p=0.751 > α=0.05), as the calculated significance level /p/ is greater than the accepted risk of error of 5%.

Upon registering brain death, it is noteworthy to observe an almost uniform distribution among patients with hypo-, normo-, and hypercalcemia.

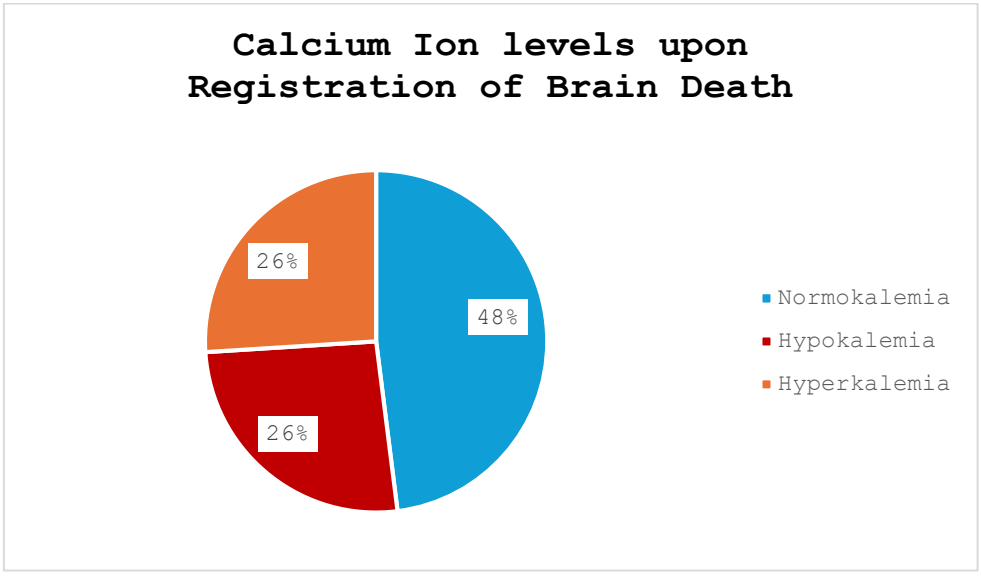


Figure 31: Calcium Ion levels upon Registration of Brain Death

The exact mechanism behind the development of hypocalcemia in cases of brain death remains unclear. Fulgenico, J P et al. reported similar deviations from reference values in patients with confirmed brain death. They found that 91% of the patients in their sample had a decrease in the plasma concentration of total calcium, but only 35% of them exhibited a decrease in ionized calcium (Fulgenico et al., 1995).

As mentioned earlier, the causes for these decreased values can be varied. Some of them, such as accompanying diseases related to the parathyroid glands and the performance of blood transfusions, could be ruled out for the participants in the present study since no information about these two factors was found in the medical documentation of any patient.

It was previously noted that hypomagnesemia was recorded in only 1.4% (n=1) of cases, which helps to exclude it as a factor leading to hypocalcemia. However, literature does provide data on a similar etiology of the condition (Orrenius et al., 2003).

One of the main reasons for the aforementioned changes in ionized calcium values could be the development of diabetes insipidus in a very high percentage (91.8%) of our patients. Several studies confirm its association with the development of hypocalcemia due to hyperosmolality and osmotic diuresis (Anwar et al., 2019; Cyprus Journal of Medical Sciences, 2023; Murthy et al., 2009; Yoshikawa et al., 2021).

Marino, P L et al. mention renal insufficiency as another possible cause for decreased levels of ionized calcium (Marino et al., 2014). Similarly, it was recorded in 10 (13.7%) patients in the representative sample. The data are presented in Table 28.

Acute kidney failure

Acute kidney failure		
Yes	13.7 %	13.7 %
No	86.3 %	100.0 %

The same team also reports a connection between the development of alkalosis and hypocalcemia (Kotoff et al., 2015). Powner, D J et al. also report such etiology of hypocalcemia (Powner et al., 2000). Therefore, our team tracked whether such a condition was observed among the patients included in the study. Table 29 shows that the condition is observed in a relatively small proportion of them - 14 (19.2%).

Development of respiratory alkalosis

Development of respiratory alkalosis		
Yes	19.2 %	19.2 %
No	80.8 %	100.0 %

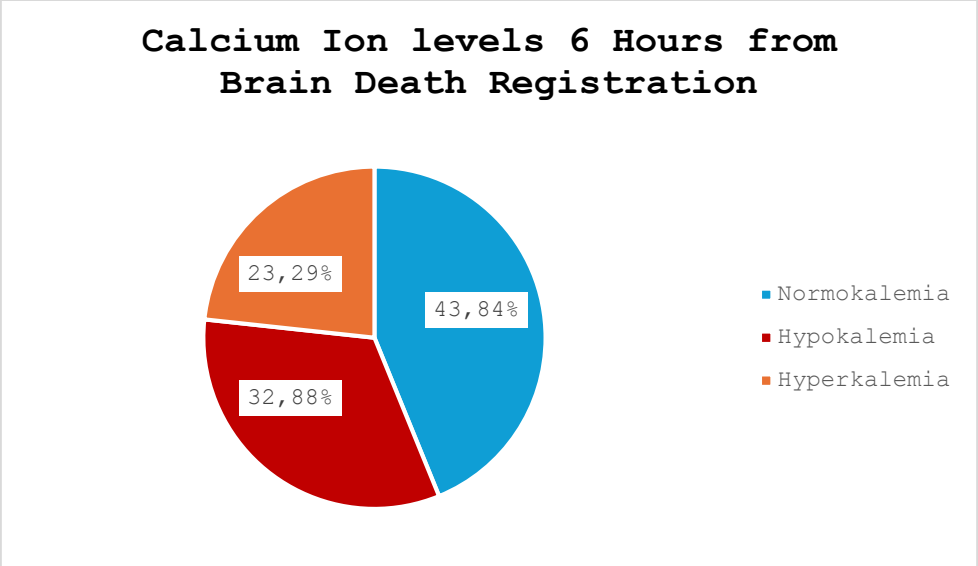
Powner, D J et al. mention in one of their articles a possible connection between the occurrence of septic conditions and decreased concentrations of calcium cations (Powner et al., 2000). Similarly, this was

recorded in only 13.7% of the patients, which does not exclude the possibility of a connection between the two conditions.

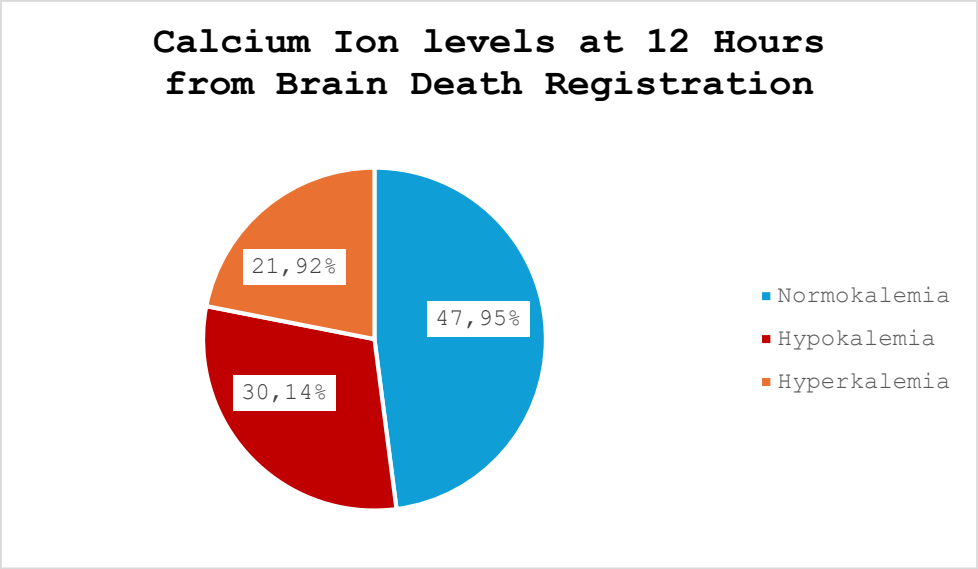
Sepsis

Sepsis		
Yes	13.7 %	13.7 %
No	86.3 %	100.0 %

In the subsequent two follow-ups of ionized calcium values over 6 hours, a similar number of cases with hypocalcemia are observed. At the 6th hour after the registration of brain death, they account for 32.88%, and at the 12th hour – 30.14%.



Ion levels



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		Application of calcium supplement		
		No	Yes	
Diagnosis				

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A non-parametric contingency coefficient is calculated given that the two variables (factorial and resulting) between which a connection is sought are categorical, arranged on a nominal scale.

The calculated contingency coefficient of 0.501 indicates a significant strong correlation between the two variables. The coefficient can be considered statistically reliable ($p=0.000<\alpha=0.05$), given that the calculated significance level Significance /p/ is smaller than the accepted risk of error of 5%.

However, at the end of the first 24 hours after the registration of irreversible brain damage, a slight decrease in cases of decreased ionized calcium is observed, with this being compensated by the appearance of a significant number of cases with serious hypocalcemia. Graphically, these changes are represented in Figure 35, where it can be seen that 20.83% of the patients are hypocalcemic, while 19.44% have registered serious hypocalcemia. It is noted that 5.56% of the reported values exceeded those defined by us as normal.

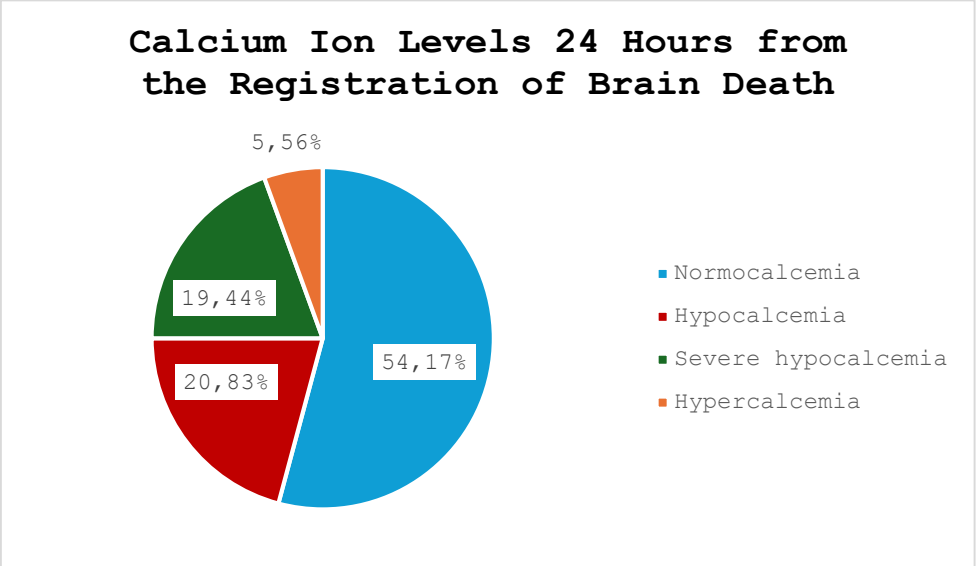

Figure 34 Calcium Ion Levels 24 Hours from the Registration of Brain Death

In an attempt to identify peak moments in the decrease of ionized calcium in patients with brain death, we compared its fluctuations across different recording periods. We found that the lowest mean value (1.14±0.256mmol/L) was observed at 24 hours from the diagnosis of brain death, when the minimum calcium value among all patients (0.6mmol/L) was also recorded. The data are presented in Table 33. The conclusions drawn were not compared with the experiences of other medical centers due to the lack of similar information in the literature.

	at hospitalization	at the time of brain death registration	6h after the diagnosis of brain death	h after the diagnosis of brain death	24h after the diagnosis of brain death

Table 33 Calcium Ion Levels During Different Monitoring Periods

5.2. Correction of Hypocalcemia.

Literature describes the possibility of correcting hypocalcemia with 10% calcium chloride or 10% calcium gluconate (Kotloff et al., 2015). Calcium replacement therapy in patients included in our study was conducted with calcium gluconate (95.5 mg/ml) in the form of 10ml ampoules. Each ampoule contains 89.4mg of calcium ions. The medication was administered slowly intravenously. As mentioned earlier, it was used in some patients before the development of brain death in connection with the treatment of their admitting diagnosis. We assume it was part of their therapy due to its key role in the coagulation cascade. After analyzing the therapy administered to patients in the representative sample, we found that calcium preparation was used in 46.6% of them.

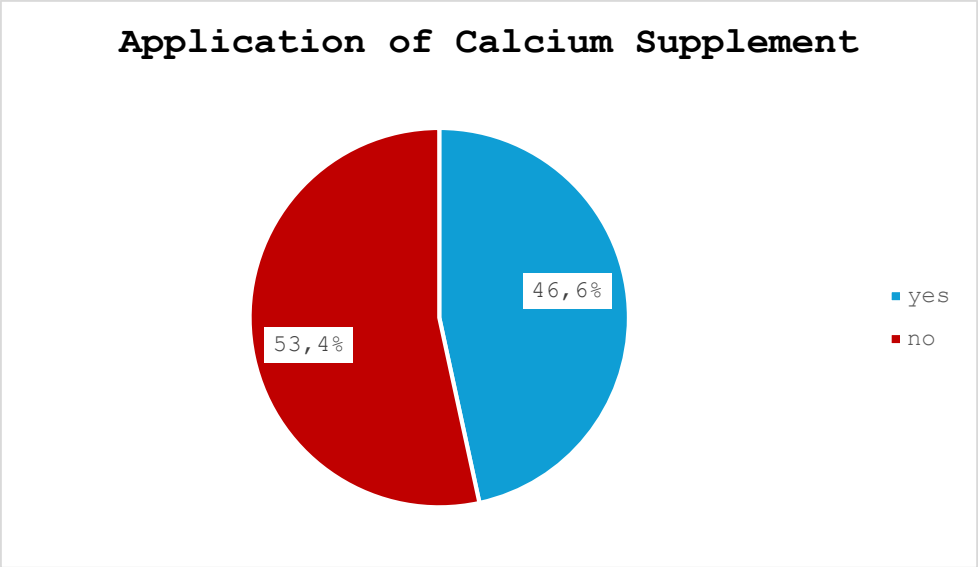

Figure 35 Application of Calcium Supplement

Calcium gluconate was administered twice daily as a bolus, dissolved in 100ml of 0.9% saline solution over 5-10 minutes. Marino, P L et al. recommend a starting dose of 200mg elemental calcium given as a bolus, followed by continuous infusion at a rate of 1-2mg/kg/h for at least 6 hours (Marino et al., 2014).

6. Changes in Plasma Magnesium Cation Concentrations and Their Correction in the Intensive Care Unit

6.1. Changes in Plasma Magnesium Cation Concentrations

Another parameter under investigation is the plasma concentration of magnesium cations. According to the literature review we conducted, magnesium deficit in patients with brain death is commonly encountered, with Powner et al. associating it with osmotic diuresis or gastrointestinal losses (Powner et al., 2000). However, according to another study, magnesium deficiency may result from traumatic brain injury (Institute of Medicine (US) Committee on Nutrition, Trauma, and the Brain, 2011). Although in fewer cases, Powner et al. claim that patients with brain death may also exhibit magnesium levels exceeding its upper reference limit (Powner et al., 2000). To determine whether deviations from normal magnesium levels are observed and to track their trends, we collected information reported at the time of brain death diagnosis, as well as at 12 and 24 hours after diagnosis. There were no data available in the provided medical documentation regarding magnesium cation levels upon patient admission and at 6 hours after diagnosis, which our team attributes to the lack of routine practice for their examination in our healthcare facility. For the purpose of this study, we adopted 0.73-1.06 mmol/L as the reference range for normomagnesemia. Any values exceeding the upper limit are considered hypermagnesemia, and those below the lower limit are considered hypomagnesemia. Literature data defining hypomagnesemia are conflicting. Some indicate hypomagnesemia at a serum magnesium concentration ≤0.61 mmol/L (1.5 mg/dL) (Guerrero-Romero et al., 2004; Hashizume et al., 1990; Wong et al., 1983), while others report it at magnesium levels ≤0.75 mmol/L (Chernnow et al., 1989; Whang et al., 1990). After analyzing the collected information from patient medical records, we found that the recorded data differ to some extent from those described in the study by Powner et al. mentioned earlier. More than half of the patients in the study (59.42%) had normal serum magnesium values at the time of

brain death diagnosis. It is noteworthy that only 10.14% (n=7) had values lower than 0.73 mmol/L, and hypermagnesemia was recorded in approximately 30% of the patients. The data are presented in Figure 36:

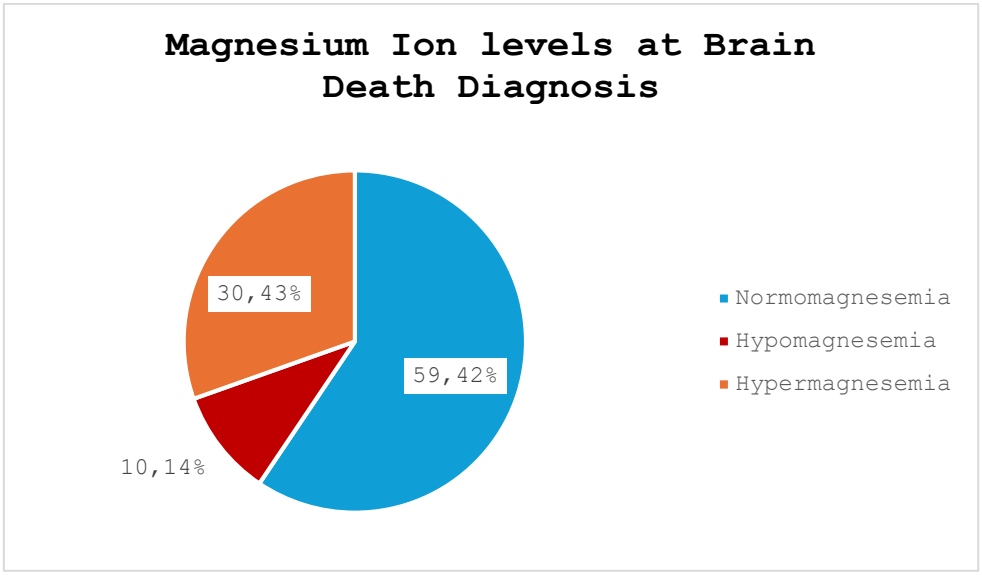

Figure 36 Magnesium Ion levels at Brain Death Diagnosis

These results differ from the published information by Marino, P L et al., who claim that magnesium excess is much less common than its deficit, with hypermagnesemia observed in only 5% of hospitalized patients (Marino et al., 2014). The same trend persists in the subsequent stages of serum magnesium monitoring at 12 and 24 hours, graphically represented in Figure 37 and Figure 38:

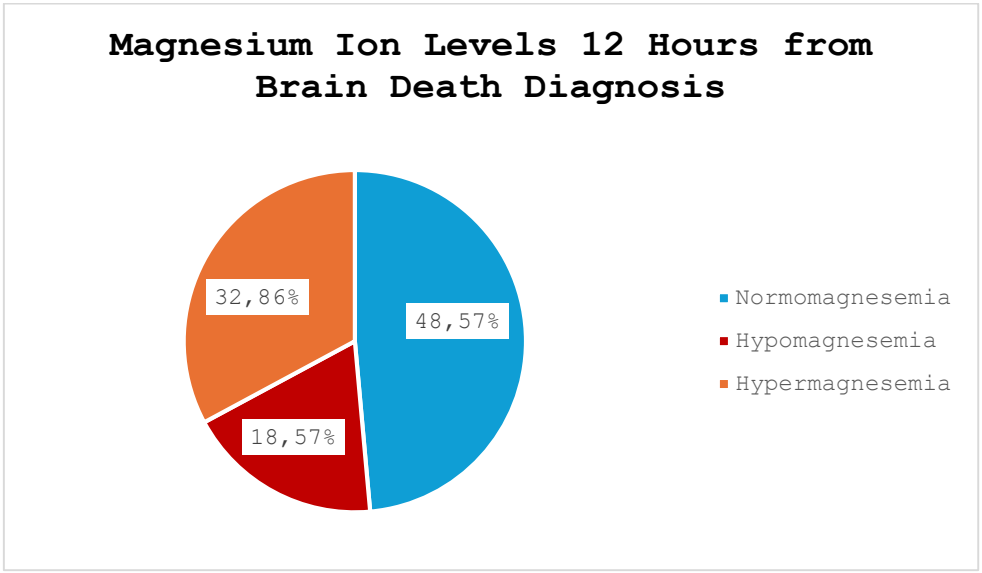

Figure 37 Magnesium Ion Levels 12 Hours from Brain Death Diagnosis

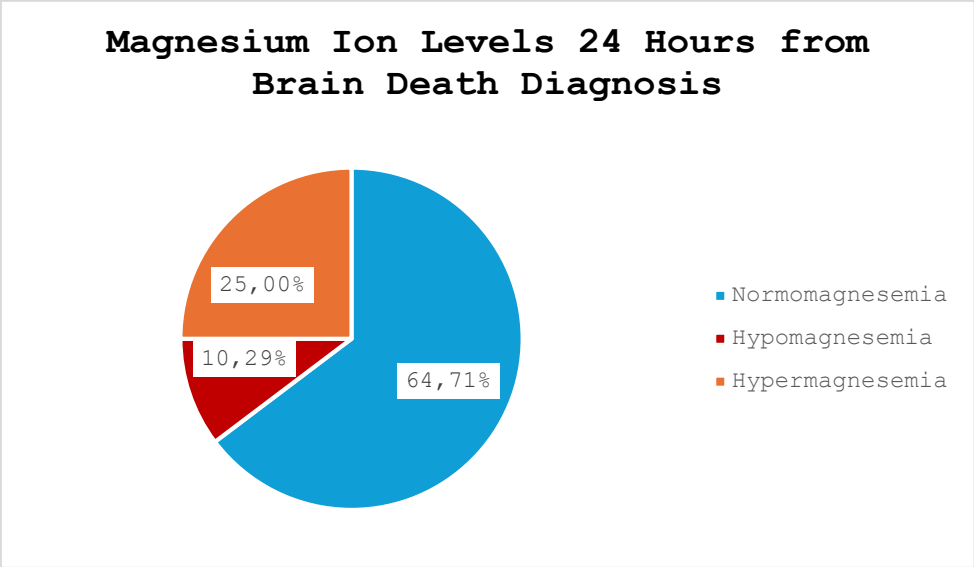

Figure 3 Magnesium Ion Levels 24 Hours from Brain Death Diagnosis

y a weak, statistically insignificant relationship exists between the etiology of the process and changes in serum magnesium ($p=0.098>\alpha=0.05$).

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Magnesium on 24h hour		
H y		H y

Diagnosis					

Table 34 Magnesium Ion Levels Depending on the Etiology of the Process

Table 35 Magnesium Ion Levels Depending on the Etiology of the Process

Regarding patients with registered normomagnesemia, no particular dynamics are observed, as it is encountered in about 30% of all patients in all reporting periods. Surprisingly high percentages registered in hypermagnesemia are most likely due to impaired kidney function since none of the patients had been registered using a magnesium preparation, which rules out the possibility of iatrogenic etiology of the deviation.

Table 36 presents in a summarized form the values of potassium ions depending on the stage of their examination. The lowest mean value (0.995±0.282 mmol/L) was registered at the diagnosis of brain death, and the lowest values (0.40 mmol/L) were reported in the following two tracking stages. On the 12th, the highest mean value (0.998±0.975 mmol/L) was recorded, while the highest value was measured at the registration of brain death (2.10 mmol/L). There is a lack of data in the available medical literature on the movement of serum magnesium by hours in patients diagnosed with brain death to compare the documented results.

	at the time of brain death diagnosis	**h after the diagnosis of brain death**	**24 after the diagnosis of brain death**

	at the time of brain death diagnosis	h after the diagnosis of brain death	24 after the diagnosis of brain death

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6.2. Correction of Hypo- and Hypermagnesemia.

As mentioned earlier, none of the patients included in the sample received a magnesium preparation in their therapy. A probable explanation could be the administration of etiological treatment leading to hypomagnesemia. Regarding hypermagnesemia, we believe that correction did not involve dialysis treatment. Dialysis was performed only in one of all patients, most likely in relation to their underlying condition.

In cases of advanced hypermagnesemia with preserved renal function, aggressive fluid resuscitation combined with furosemide is possible. Therefore, we tracked the amount of fluid-electrolyte solutions used in the patients in the sample and the cases requiring diuresis stimulation.

Table 37 clearly shows that the average amount of fluid-electrolyte solutions used at the registration of brain death is 20 ml/kg. The variation in this characteristic is about 7 ml/kg, with the minimum quantity being 12 ml/kg and the maximum being 40 ml/kg.

Table 37 Fluid-Electrolyte Solutions Administered at the Time of Brain Death Registration (ml/kg)

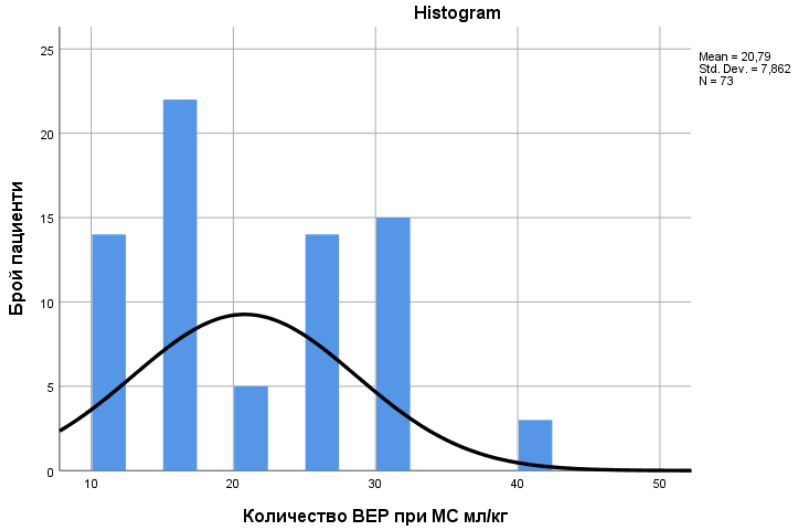

Figure 39 Histogram of Fluid-Electrolyte Solutions Administered at the Time of Brain Death Registration

After the diagnosis, significant changes in the quantity of fluid-electrolyte solutions included in patient therapy are observed. From Table 38, it can be observed that their average quantity increases to almost 60 ml/kg. The variation in this parameter is around 26 ml/kg, with the smallest administered quantity being 15 ml/kg, and the largest being 120 ml/kg.

Statistics

Quantity of Fluid-Electrolyte Solutions after the Time of Brain Death Registration (ml/kg)

N	Valid	73
	Missing	0
Mean		57,53

Std. Deviation	26,248
Skewness	,441
Std. Error of Skewness	,281
Kurtosis	-,719
Std. Error of Kurtosis	,555
Minimum	15
Maximum	120

Table 38: Quantity of fluid-electrolyte solutions administered after brain death registration (ml/kg)

The distribution based on this parameter exhibits moderate asymmetry, as shown in the following histogram:

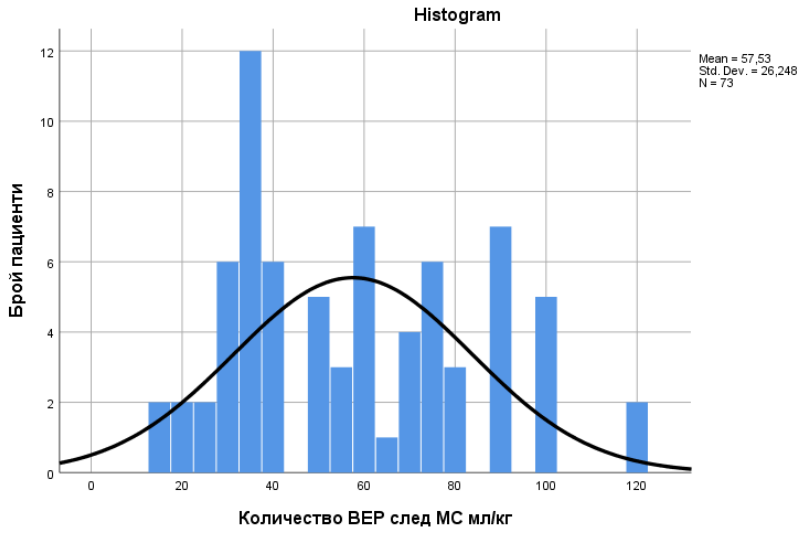

Figure 40: Amount of fluid-electrolyte solutions administered at the time of brain death registration (ml/kg)

In less than half of the patients (35.2%), diuresis stimulation was necessary, utilizing Furantil in the form of bolus doses or continuous infusion. Table 39 outlines the prescribed doses, with intravenous bolus administration being the preferred method, most commonly applying 20mg of the medication every 12 hours.

Application of Furanthril

Application of Furanthril		
y e	5.6 %	5.6 %
y e	2.8 %	8.5 %
yes, 2x10mg	2.8 %	11.3 %
yes, 2x20mg	18.3 %	29.6 %
yes, 3x20mg	2.8 %	32.4 %
y e	1.4 %	33.8 %
y e	1.4 %	35.2 %
no	64.8 %	100.0 %

Table 39: Administration of Furantil

7. Changes in plasma concentration of inorganic phosphorus and its correction in the intensive care unit.

7.1. Changes in plasma concentration of inorganic phosphorus.

Young, G.B. et al. consider that the normal functioning of neurons and the release of oxygen to the already damaged brain tissue of a patient in brain death depend on the normal concentration of inorganic phosphorus (Young et al., 1982). In connection with this, we traced its trends in the serum of patients included in the study. Inorganic phosphorus is not part of the routine panel of laboratory tests performed in our medical center, which is why we managed to gather information about its changes only at two stages - upon registration of brain death and 24 hours thereafter. We adopted reference values in the range of 0.81-1.45 mmol/L as normophosphatemia. All results exceeding the upper limit were defined as hyperphosphatemia. Values lower than 0.81 mmol/L were divided into two groups - patients with hypophosphatemia (with measured values between 0.81 and 0.30 mmol/L) and patients with severe hypophosphatemia (with measured values below 0.30 mmol/L).

After processing the collected information, we found that more than half of the patients (65.67%) included in the study had normal phosphorus levels at the time of brain death diagnosis. Figure 41 shows that nearly 30% of them exhibited hypophosphatemia, while the remaining small percentages were distributed among cases of severe hypophosphatemia and hyperphosphatemia.

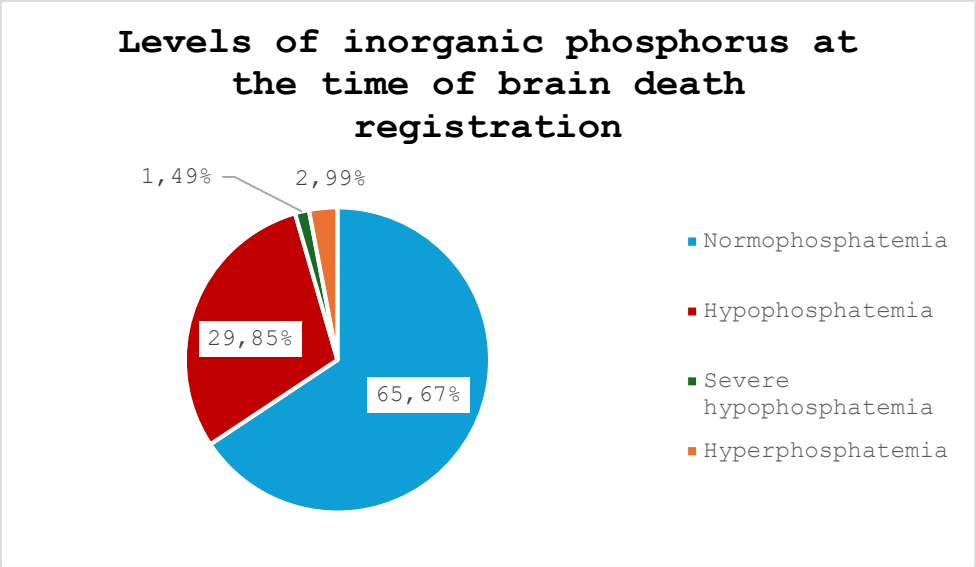

Figure 41: Levels of inorganic phosphorus at the time of brain death registration

Over the next 24 hours, the number of patients with severe hypophosphatemia and hyperphosphatemia remains unchanged compared to the previous day. Figure 42 shows a decrease in serum phosphorus in more than half of the patients who were normophosphatemic in the previous reporting period. Thus, the percentage of representatives in the sample with registered low serum phosphorus levels increases to 61.19%, and this change occurs entirely at the expense of normophosphatemic patients.

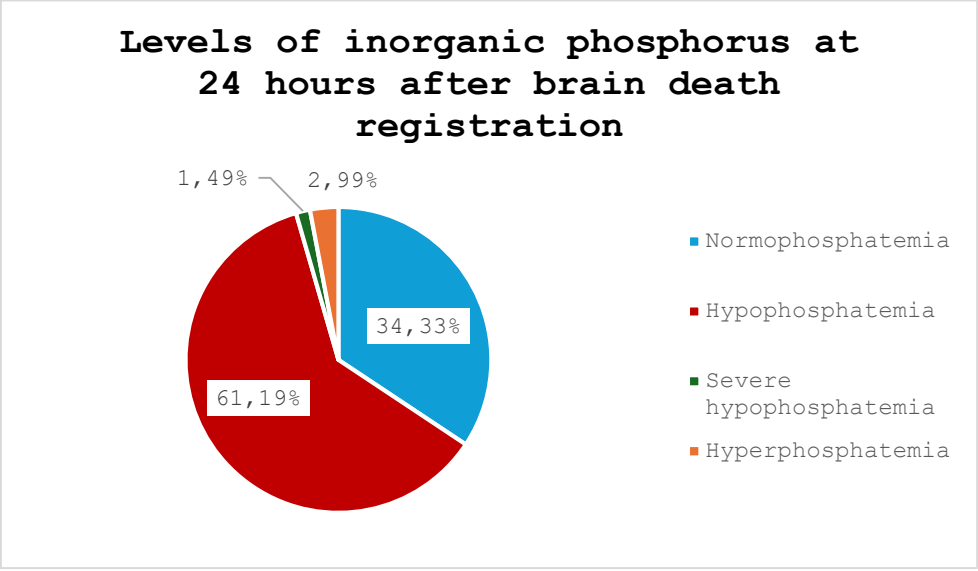

Figure 42: Levels of inorganic phosphorus at 24 hours after brain death registration

Similar findings are reported by Riou, B et al., who found that 67% (n=60) of 90 patients with brain death had low phosphorus levels. Among them, 24% had mild hypophosphatemia, and 42% had severe hypophosphatemia (Riou et al., 1995). Dominguez-Roldan, J M et al. also reported a large number of

Symmetric Measures

		Value	Approximate Significance
Nominal by Nominal	Contingency Coefficient	,401	,800
N of Valid Cases		67	

patients with brain death who had low phosphorus levels, with an even higher percentage - 72% of all participants in the study (Dominguez-Roldan et al., 2005).

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		Inorganic Phosphorus at 24h				
		Hypophosphatemia	Normophosphatemia	Hyper-phosphatemia	Serious hyperphosphatemia	
Diagnosis						

We attempted to find a link between the development of hypophosphatemia and the cause of brain death. As seen in Tables 40 and 41, we were only able to register a moderate statistically insignificant one ($p=0.800>\alpha=0.05$).

Table 40: Inorganic Phosphorus Values Depending on the Etiology of the Process

Table 41: Inorganic Phosphorus Values Depending on the Etiology of the Process

According to Anwar, A.S.M. Tanim, and Jae-Myeong Lee, low serum phosphorus levels in patients who have experienced brain death are attributed to the development of untreated diabetes insipidus (Anwar et al., 2019). Additionally, Powner, D.J. et al. suggest that other contributing factors may include gastrointestinal losses, respiratory alkalosis, administration of dextrose or insulin (Power et al., 1995; Powner et al., 2000; Riou et al., 1995). Furthermore, literature mentions a similar effect resulting from hyperglycemia or administration of catecholamines (Riou et al., 1995).

As previously mentioned, nearly 92% of all 73 patients had registered diabetes insipidus, which may be associated with the development of hypophosphatemia.

According to literature, another possible explanation for these changes in fluid and electrolyte balance could be respiratory alkalosis, observed in almost 20% (n=14) of patients in the representative sample. The data are presented in Table 42.

Development of respiratory alkalosis

Development of respiratory alkalosis		
Yes	19.2 %	19.2 %
No	80.8 %	100.0 %

Table 43 reveals that nearly 30% of the patients experienced gastrointestinal losses, which also could have contributed to lowering serum phosphate levels below its lower reference range.

Yes	27.4 %	27.4 %
No	72.6 %	100.0 %

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Our team dismisses the likelihood of such etiology for hypophosphatemia, as the data were collected from the medical documentation's anamnestic records regarding losses that occurred before the hospitalization of the patients. The current changes in the electrolyte balance reflect the patients' condition at the time of diagnosing brain death and at the 24-hour mark thereafter.

We also tracked the administration of catecholamines among the participants included in the analysis. Given the hemodynamic instability of the patients, this type of medication is often part of their therapy. Table 44 illustrates that all 73 patients received medications to support their cardiovascular function, with some receiving monotherapy and others a combination of medications.

Application of catecholmines

	Yes, Dopamine				
	Yes, Dopamine+NA				
	Yes, Dopamine+Dobutamine+NA				
	Yes, Dopamine+Dobutamine				
	Yes, Dopamine+A				
	Yes, Dopamine+Dobutamine+A				
	Yes, Dopamine+Dobutamine+NA+A				
	Yes, Dopamine+NA+A				

Table 44: Application of Catecholamines

These results are graphically presented in Figure 43, where it is evident that the most common choice of conditioning medication by the attending physician has been Dopamine. It has been used alone in more than half of the patients (63.01%).

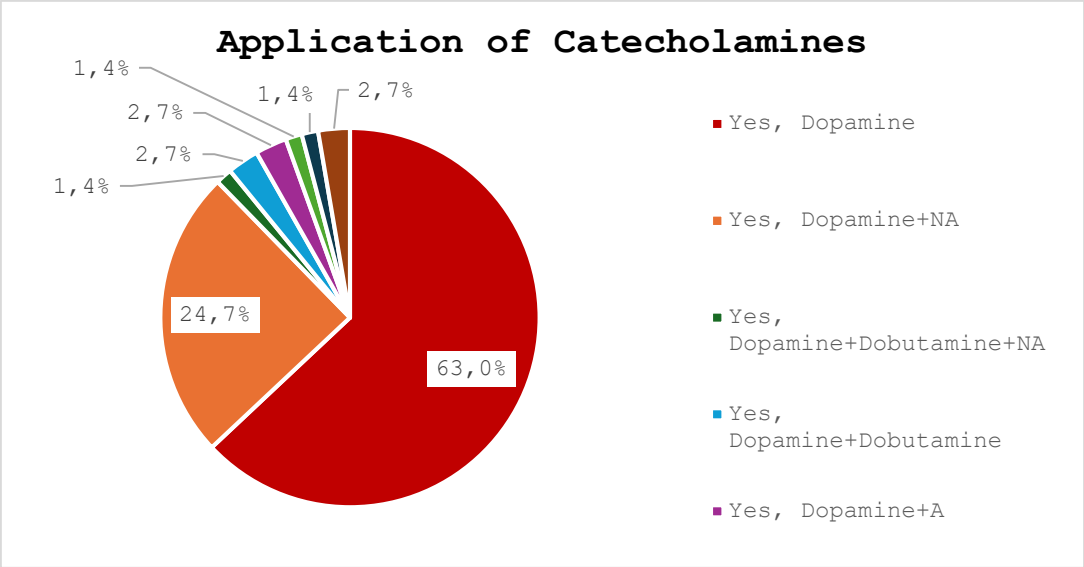

Table 45: Application of Catecholamines

The second most used option in this particular group of patients was the combination of Dopamine with Norepinephrine, used in almost a quarter of the participants in the study (24.66%). From the graph, it can be seen that although in fewer cases Dobutamine or Adrenaline were used as supportive agents for cardiovascular function.

The high percentage of exogenous catecholamine application may explain the decrease in serum phosphorus in this particular study.

In summary, the serum phosphorus values recorded at the time of diagnosis of brain death and 24 hours thereafter are presented in Table 45. The lowest mean value (0.84 ±0.32 mmol/L) was recorded at the second stage of monitoring serum concentrations. In the same period, the highest value was measured in all patients - 2.05 mmol/L. The lowest value persisting in both periods was -0.1 mmol/L. There are no literature data on the experience of other medical centers regarding trends in changes in serum phosphorus levels in patients with brain death over time. We managed to find information only about the lowest values for hypophosphatemia (0.56 mmol/L) and severe hypophosphatemia (0.25 mmol/L), recorded by Riou, B et al. in their study (Riou et al., 1995).

	P at the time of brain death registration	24h after the diagnosis of brain death

Table 45 Inorganic Phosphorus Values During Different Follow-up Periods

7.2. Correction of Hypophosphatemia.

According to the provided medical documentation, none of the patients in the studied population received a phosphorus-containing medication for the correction of hypophosphatemia.

8. Study Limitations.

When interpreting and applying the results and conclusions obtained from this study, some potential limitations should be considered. The study design is retrospective, using a non-randomized selection of patients and lacking a control group. The data were collected from a single medical center with a relatively large capacity for the country. Therefore, it could be assumed that a large number of patients pass through it, and the medical teams involved in conditioning organ donors with brain death have years of experience in the specific field. Consequently, conditions in smaller medical centers may vary significantly.

The pathology examined in this study occurs relatively rarely compared to many other conditions, so the number of patients included in the representative sample is relatively small despite the large time interval tracked. This may be considered as a reason for the relatively low frequency of occurrences and their correction.

Another possible limitation is the quality of the data collected from the provided medical documentation. Much of the data were gathered from manually entered patient records, which creates conditions for omitting some information and making errors. Additionally, information about some of the planned

intervals for recording the indicators is lacking in the medical documentation, or their quality does not allow them to be analyzed and included in the study.

9. Conclusion.

In our conducted retrospective clinical study, we tracked changes in the water-electrolyte balance in patients who experienced brain death and were managed as potential organ donors. It encompassed 73 patients with proven brain death over six years. There is a relatively even distribution by gender, with 47.9% being female and the remaining 52.1% being male. The mean age of the patients included in the study is 47 years.

Various etiological factors of the process were registered with the following frequency of occurrence:

Etiology of Brain Death:	**Frequency (%)**
Hemorrhagic stroke	45,2
Subarachnoid hemorrhage	27,4
Neoplastic process	6,8
Infectious disease	1,4
Traumatic brain injury	2,7
Methanol poisoning	1,4
Ischemic stroke	15,1

Table 46 Etiology of Brain Death

Frequency of the development of central diabetes insipidus among the patients in the sample was tracked based on clinical and paraclinical indicators. The reported results are similar to those described in available medical literature, with this particular study showing its occurrence in 91.8% of cases.

A common deviation in the water-electrolyte balance among organ donors with brain death is hypernatremia. To track how many patients experience similar changes, we monitored serum sodium levels during patient hospitalization, at the time of brain death diagnosis, as well as at 6, 12, and 24 hours thereafter. The results are as follows:

Period of Hypernatremia Registration:	**Frequency (%)**
Upon hospitalization	6,85
At the time of diagnosis of brain death	62,5
At 6 hours after diagnosis of brain death	59,72
At 12 hours after diagnosis of brain death	67,12
At 24 hours after diagnosis of brain death	68,49

Table 47 Frequency of Hypernatremia by Periods

The highest mean serum sodium values (152±14.4 mmol/L) were recorded at the time of brain death registration, when the highest values were also measured during monitoring – 198 mmol/L.

It is noteworthy that hyponatremia was observed among patients at 24 hours with the lowest values recorded at 113 mmol/L.

After analyzing the provided medical documentation, we found that the following interventions were used to address hypernatremia:

- Replacement therapy with Minirin (Desmopressin acetate) at a dose of 0.1 mg when diuresis exceeded 400 ml/h in 43.8% of patients.

- Oral administration of distilled water through a nasogastric tube six times over 24 hours at a dose of 200 ml in 54.8% of all patients.

- Administration of electrolyte solutions containing glucose (Sol. Glucosae 5%, Sol. Glucosae 10%) in 89% of all patients.

Another parameter we tracked was the serum chloride levels, during the same intervals as sodium – at hospitalization of patients, upon registration of brain death, as well as at 6th, 12th, and 24th hour thereafter. We observed the following results:

Period of Hyperchloremia	**Frequency (%)**
At hospitalization	8,22
Upon registration of brain death	56,2
At 6th hour from the registration of brain death	50,7
At 12th hour from the registration of brain death	72,6
At 24th hour from the registration of brain death	60,3

Table 48 Frequency of Hyperchloremia by Periods

The highest average serum chloride values were measured upon registration of brain death and at the 12th hour thereafter (114±12.5mmol/L and 114±7.52mmol/L, respectively). The highest recorded value was observed upon diagnosing brain death - 153mmol/L.

To correct the observed changes, etiological treatment was implemented, including the initiation of replacement therapy with Minirin. Bicarbonate administration was observed in 9.6% of patients, with two of them administered during cardio-pulmonary resuscitation. Vitamin D was not administered to any of the patients.

Another characteristic deviation in the water-electrolyte balance of patients with brain death is hypokalemia. Therefore, we tracked the serum potassium values upon hospitalization of patients, upon diagnosing brain death, as well as at the 6th, 12th, and 24th hour thereafter. Upon analyzing the collected data, we observed the following changes:

Period of Hypokalemia Registration	**Frequency (%)**
Upon hospitalization	30,14
Upon diagnosis of brain death	52,06
At 6 hours from the diagnosis of brain death	57,54
At 12 hours from the diagnosis of brain death	52,06
At 24 hours from the diagnosis of brain death	43,84

The lowest average value was recorded at 6 hours into the monitoring (9.48 ± 0.816 mmol/L), and the lowest measured value (1.3 mmol/L) was at the diagnosis of brain death and 6 hours thereafter. To address hypokalemia, replacement therapy with potassium chloride at a concentration of 2 mmol/ml was administered. Medical documentation indicates this therapy was part of the treatment for 75.3% of the patients included in the study. The most commonly used dose ranged between 3.2 and 4 mmol/h.

To determine if there were changes in the concentration of calcium ions and what they were, we tracked their concentrations upon patient hospitalization, upon diagnosis of brain death, and at 6, 12, and 24 hours after diagnosis. The results are as follows:

Period of Hypocalcemia Registration	**Frequency (%)**
Upon hospitalization	47,95
Upon diagnosis of brain death	32
At 6 hours from the diagnosis of brain death	32,88
At 12 hours from the diagnosis of brain death	30,14
At 24 hours from the diagnosis of brain death	40,27

Table 50 Frequency of Hypomagnesemia by Periods.

The lowest mean value (1.14±0.256mmol/L) and the lowest measured value (0.6mmol/L) were recorded at the 24th hour after the diagnosis of brain death. The presence of diabetes insipidus was considered the most likely cause of hypomagnesemia.

To correct the hypomagnesemia, calcium gluconate was used in our facility. We found that it was part of the therapy for 46.6% of the patients, with some patients receiving it before the development of brain death.

We did not find definitive data in the medical literature regarding changes in serum magnesium levels in patients with brain death during their conditioning. Therefore, we collected information on measured values at the time of diagnosis of brain death, as well as at the 12th and 24th hour from the diagnosis, which we subjected to analysis. Over the three tracked periods, the percentage of patients with hypomagnesemia was lower compared to those with hypermagnesemia. The frequency of occurrence for both deviations is as follows:

Period of Hypomagnesemia Registration	**Frequency of Hypomagnesemia (%)**	**Frequency of Hypermagnesemia (%)**
At Brain Death Registration	10,14	30,43
At 12 Hours from Brain Death Registration	18,57	32,86
At 24 Hours from Brain Death Registration	10,29	25

Table 51 Frequency of Serum Magnesium Deviations.

The lowest mean value (0.995±0.282 mmol/L) was observed at the time of diagnosing brain death, while the lowest recorded values (0.40 mmol/L) were detected in the subsequent two periods of observation. The highest mean value (0.998±0.975 mmol/L) was observed at the 12th hour, with the highest recorded value (2.10 mmol/L) measured at the time of diagnosing brain death.

None of the patients included in the study had received magnesium supplementation. Dialysis treatment was not employed in correcting hypermagnesemia.

The last parameter we tracked in our sample was the serum concentration of inorganic phosphorus. Since this is not routinely tested in our intensive care unit, we could only gather data on its values at the time of diagnosing brain death and 24 hours later. Hypophosphatemia was registered as follows:

- 31.34% at the time of diagnosing brain death

- 62.68% at 24 hours after diagnosing brain death

The lowest mean value of inorganic phosphorus was recorded 24 hours after diagnosing brain death, with a value of 0.84±0.32 mmol/L. The lowest persisting value in both periods was -0.1 mmol/L. None of the patients received phosphorus-containing drugs for correction.

Based on our results, our center's practices, and data from the literature review, we developed the following algorithm for correcting changes in water-electrolyte balance and management of potential brain-dead donors:

1. Laboratory testing of serum ions (sodium, potassium, chloride, calcium, magnesium, inorganic phosphorus) and urine (sediment) urgently. Monitoring every 4 hours.

2. Central venous access and at least one wide peripheral access.

3. Arterial line for blood gas analysis and invasive pressure assessment.

4. Monitoring hourly diuresis.

5. Early recognition and diagnosis of diabetes insipidus based on clinical and paraclinical indicators:

- Polyuria (diuresis > 2 ml/kg/h)

- Urine specific gravity < 1.005 g/ml

- Hypernatremia (Na^+ > 145 mmol/L)

Therapy (titrated to achieve diuresis below 3 ml/kg/h) for diabetes insipidus:

- Minirin (Desmopressin acetate) tablets 0.2 mg – application of 0.1 mg via nasogastric tube until diuresis falls below 3 ml/kg/h, with strict control of urine losses and electrolyte monitoring.

6. Ensuring normovolemia and correcting hypernatremia through:

- Calculating the patient's water deficit

- Infusion therapy with electrolyte solutions containing glucose (Sol. Glucosae 5% and Sol. Glucosae 10%) at a dose of 6.25-37.5 ml/kg/24h

- Administering pure water through a nasogastric tube at a rate of 200 ml every 4 hours

Monitoring central venous pressure, water-electrolyte balance, and blood sugar levels.

7. Correcting hyperchloremia by administering bicarbonates at a dose of 5-15 mmol/kg/24h in combination with potassium preparations.

8. Correcting hypokalemia by conducting prolonged infusion of potassium chloride at a dose of 3.2-4 mmol/h, depending on laboratory parameters. The maximum infusion rate is 20 mmol/h, but in case of serum potassium below 1 mmol/L or serious arrhythmia, a rate of 40 mmol/h is used.

- Using a large, central vein is preferred for infusion

- With infusion rates exceeding 20 mmol/h, upper limb veins should not be used due to a rapid increase in K+ in the right half of the heart, leading to asystole.

9. Ensuring normocalcemia by conducting replacement therapy with 10% calcium gluconate, administered slowly intravenously every 12 hours, with strict control of serum ionized calcium levels. Due to a decrease in total calcium levels within 30 minutes, a prolonged infusion at a rate of 1-2 mg/kg/h for at least 6 hours is recommended.

10. Deviations from normomagnesemia are corrected depending on their nature:

- For moderate hypomagnesemia (serum Mg < 1 mmol/l), start with the infusion of 6 g of $MgSO_4$ dissolved in isotonic solution over 3 hours, followed by another 5 g of $MgSO_4$ over 6 hours. Over the next 5 days, administer 5 g of $MgSO_4$ as a prolonged infusion every 12 hours.

• For life-threatening hypomagnesemia (manifesting as cardiac arrhythmias and generalized seizures), administer 2g of $MgSO_4$ over 2-5 minutes, followed by an infusion of 5g of $MgSO_4$. Continue with a prolonged infusion of 5g of $MgSO_4$ every 12 hours for the next 5 days.

• In symptomatic hypermagnesemia, administer 1g of calcium gluconate intravenously over 2-3 minutes.

11.Phosphate replacement is performed for severe hypophosphatemia (<0.3 mmol/L). Depending on the patient's body weight, the dose ranges from 30 to 50 mmol.

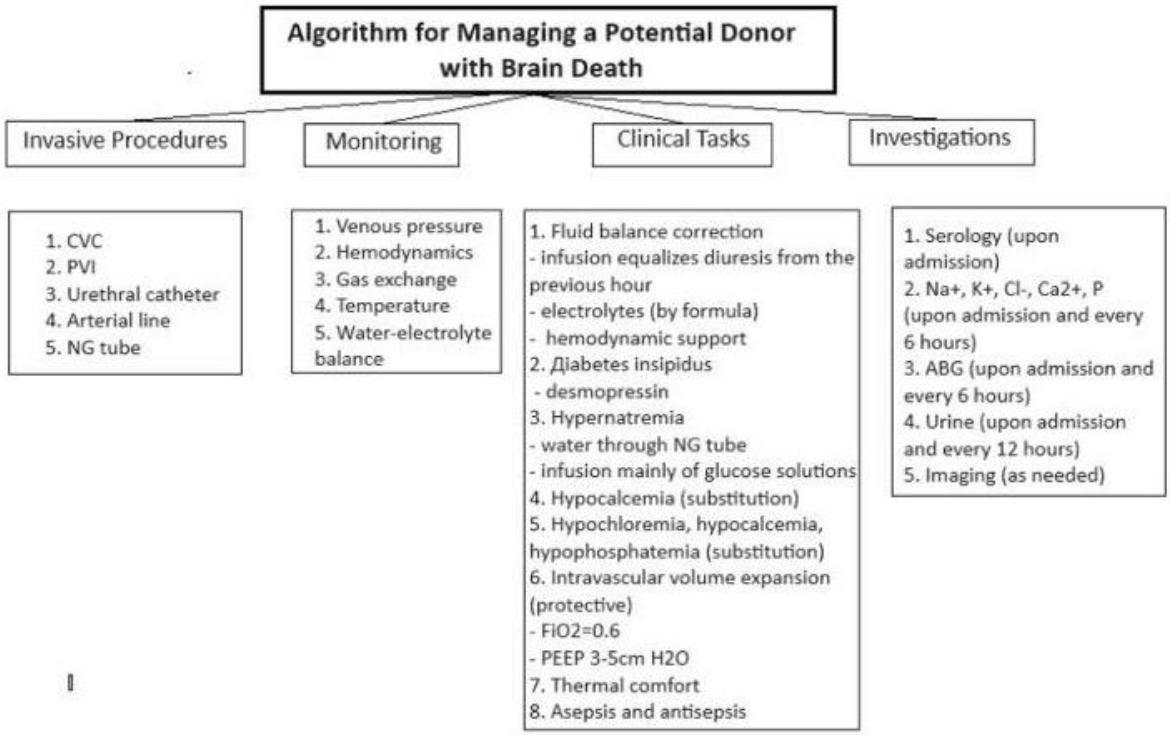

Figure 44: Algorithm for Management of Potential Organ Donor with Brain Death

V. Conclusions

1. The number of patients diagnosed with brain death in our cohort gradually decreases, necessitating the activation of identification and initiation of the conditioning process.

2. We observe a high frequency of developing diabetes insipidus, which we consider a primary factor for changes in water-electrolyte balance.

3. Hypernatremia and hyperchloremia were registered in more than 50% of patients in every period following the diagnosis of brain death.

4. Hypokalemia remains one of the most challenging deviations in water-electrolyte balance to control, as despite replacement therapy, the number of patients with hypokalemia persists and the proportion of those with severe hypokalemia increases.

5. A large percentage of patients maintain normal serum calcium levels.

6. Regular monitoring of serum magnesium and inorganic phosphate is necessary.

VI. Contributions

1. For the first time in Bulgaria, a comprehensive analysis of water-electrolyte changes in organ donors with brain death is conducted.

2. The most likely causes of these deviations are analyzed for the first time.

3. The methods for correcting changes in water-electrolyte balance in organ donors with brain death are tracked for the first time.

4. A comparison between the methods of correcting water-electrolyte deviations in Bulgaria and those in foreign medical centers is made for the first time.

VII. Scientific Publications Related to the Dissertation Work

1. "Influence of Hypernatremia on the Function of Liver Transplantation in Organ Donors with Brain Death"

B. Georgieva, B. Naydenova

Varna Medical Forum vol. 12, 2023, issue 2, pp. 27-38

Link to the full text of the article:

https://journals.mu-varna.bg/index.php/vmf/article/view/9338

2. "Clinical Factors and Instrumental Studies Used in Modern Clinical Practice for Diagnosing Brain Death"

B. Georgieva, B. Naydenova

Varna Medical Forum vol. 12, 2023, issue 2, pp. 27-38

Link to the full text of the article:

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