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# Predictive Value of Blood N-Terminal Pro-Brain Natriuretic Peptide Concentrations for Early Patent Ductus Closure in Very Preterm Infants

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## Abstract

**Objectives:** It has been shown that blood concentrations of NT-proBNP may be useful in identifying preterm infants at risk of hemodynamically significant patent ductus arteriosus and its complications. The aim of the study was to assess predictive value of serum NT-proBNP levels for early ductus arteriosus (DA) closure in very preterm newborns.

**Methods:** Fifty-two infants <32 weeks' gestation aged <72 hours with patent ductus arteriosus (PDA) diameter >1.5 mm were involved in a randomized study. Twenty-seven (52%) of them were treated with ibuprofen or paracetamol starting within the first 3 days of life. Expectant management was applied to 25 (48%) infants. All patients underwent planned echocardiographic (daily) and two serum NT-proBNP measurements within the first 10 days after birth. Depending on the DA closure within the first 10 days of life, 2 groups of patients were formed retrospectively, with closed (n = 30) or patent (n = 22) DA by this age.

**Results:** In the first 10 days of life, DA closure occurred in 19 (70%) treated infants and in 11 (44%) infants managed expectantly (p > 0,05). Initial concentrations of NT-proBNP were significantly higher in infants that had patent ductus arteriosus (PDA) at 10 days of life. By the eighth day, median NT-proBNP values in both groups significantly decreased but remained considerably higher in newborns with PDA. NT-proBNP serum concentrations on the second day of life could reliably predict DA closure within the first 10 days after birth in treated babies (the AUC was significant 0.81 [95% CI: 0.58–1.03], p < 0.05) but not in infants who were managed expectantly.

**Conclusions:** Serum NT-proBNP concentrations on the second day of life could reliably predict early PDA closure in treated but not in expectantly managed very preterm infants.

**Keywords:** NT-proBNP, Prognostic value, Patent ductus arteriosus, Very preterm infants

## 1. Introduction

Patent ductus arteriosus (PDA) is a common complication in preterm newborns, occurring in approximately 33% of very preterm and 65% of extremely preterm infants [1,2]. According to numerous studies, the persistence of PDA in this population of infants is associated with higher mortality and severe neonatal morbidity, including renal failure, intraventricular hemorrhage (IVH), pulmonary hemorrhage,

bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), and heart failure [3,4]. However, known approaches to PDA treatment do not reduce the frequency of these conditions [5,6]. Therefore, there are still many controversial and unresolved issues regarding the need for treatment and management strategies for hemodynamically significant PDA (hsPDA) [7]. Although echocardiography today is the gold standard for the diagnosis and assessment of hsPDA, echocardiographic data have insufficient prognostic

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value for spontaneous DA closure [8]. Therefore, there is an increased interest in identification of biochemical markers that are associated with PDA and PDA-associated diseases and can be used not only to confirm hsPDA but also to prove the effectiveness of treatment [9,10].

B-type natriuretic peptide (BNP) is released by ventricular cardiomyocytes in response to volume expansion and pressure overload of the heart. The pro-BNP is cleaved within cardiomyocytes into the biologically active form, BNP, and the inactive N-terminal pro-brain natriuretic peptide (NT-proBNP) fragment [11].

It has been shown that plasma BNP and NT-proBNP levels correlate well with echocardiographic markers of hsPDA [12–14]. Thus, several studies have been conducted to evaluate the usefulness of these markers in detecting PDA that requires treatment and monitors its effectiveness. Sensitivity of the corresponding values ranged between 65% and 90%, while specificity showed 55% to 85% [15–17]. The results of some studies indicate that certain BNP levels in the first days after birth can predict closure or non-closure of PDA [15–18]. However, the available data are sparse and contradictory.

The aim of the study was to assess the predictive value of serum NT-proBNP levels for DA closure in very preterm infants within the first 10 days of life depending on the strategy of care.

## 2. Methods

### 2.1. Study design and patients

In this study, we used data of 52 outborn preterm infants, who had their serum NT-proBNP concentrations measured within the first 10 days of life. These infants were enrolled in a randomized controlled trial to evaluate the comparative efficacy and safety of the early treatment and expectant management of PDA in very preterm infants (*ClinicalTrials.gov* - NCT03860428) between March 2019 and January 2020 (Fig. 1). The trial is currently underway.

The trial used the following inclusion criteria: birth weight <1500 g, gestational age (GA) < 32 weeks, age at admission to the neonatal intensive care unit (NICU) < 72 h, and PDA diameter >1.5 mm. Exclusion criteria listed a presence of congenital heart defect other than PDA, clinically apparent hemorrhagic syndrome, any IVH in the first 48 hours or IVH grade 3–4 at any time, suspected/apparent NEC or lung hypoplasia, platelet count of <50,000/mm<sup>3</sup>, oliguria <1 ml/kg/h, and absence of informed consent of the parents.

#### Abbreviation

BNP	B-type natriuretic peptide
BPD	Bronchopulmonary dysplasia
CRP	C-reactive protein
DA	Ductus arteriosus
GA	Gestational age
hsPDA	Hemodynamically significant patent ductus arteriosus
IVH	Intraventricular hemorrhage
LA/Ao	Left atrium to aortic root diameter ratio
NEC	Necrotizing enterocolitis
NICU	Neonatal intensive care unit
NT-proBNP	N-terminal pro-brain natriuretic peptide
PDA	Patent ductus arteriosus

After enrollment, the patients were randomly allocated to one of the study groups. The randomization was performed using a computer-generated random series of numbers with GraphPad software.

When the patient was allocated to the medical treatment arm, ibuprofen or paracetamol was started as soon as possible, but not later than three hours after inclusion. Twenty-seven newborns (52%) were treated with ibuprofen (n = 13) or paracetamol (n = 14) starting within the first three days of life. Ibuprofen was administered rectally in a single dose of 20/10/10 mg/kg/day for three days; paracetamol was used intravenously, 15 mg/kg/dose every six hours for three days. Echocardiographic evaluation was performed at least 12 hours after the last dose of the first course. If the DA was found to be closed, no further investigations or treatment was needed. DA was considered to be closed if it could not be visualized using color Doppler imaging or if its transductal diameter was <0.5 mm. If the DA was not closed, the second course of treatment was started at least 24 hours after the third dose of the first course [19].

Expectant management, involving clinical and echocardiographic monitoring without medical PDA treatment, was randomly applied to 25 (48%) infants. The patients in both study arms received the same treatment, except for the administration of ibuprofen or paracetamol in the treatment arm. Medically treated infants had an additional echocardiography performed after the completion of the treatment course.

According to the results of echocardiographic monitoring, two groups of patients were formed: in 30 (58%) of them, DA closed within the first 10 days of life (the early ductal closure group), and in 22 (42%) DA remained patent at 10 days of life (the persistent PDA group).

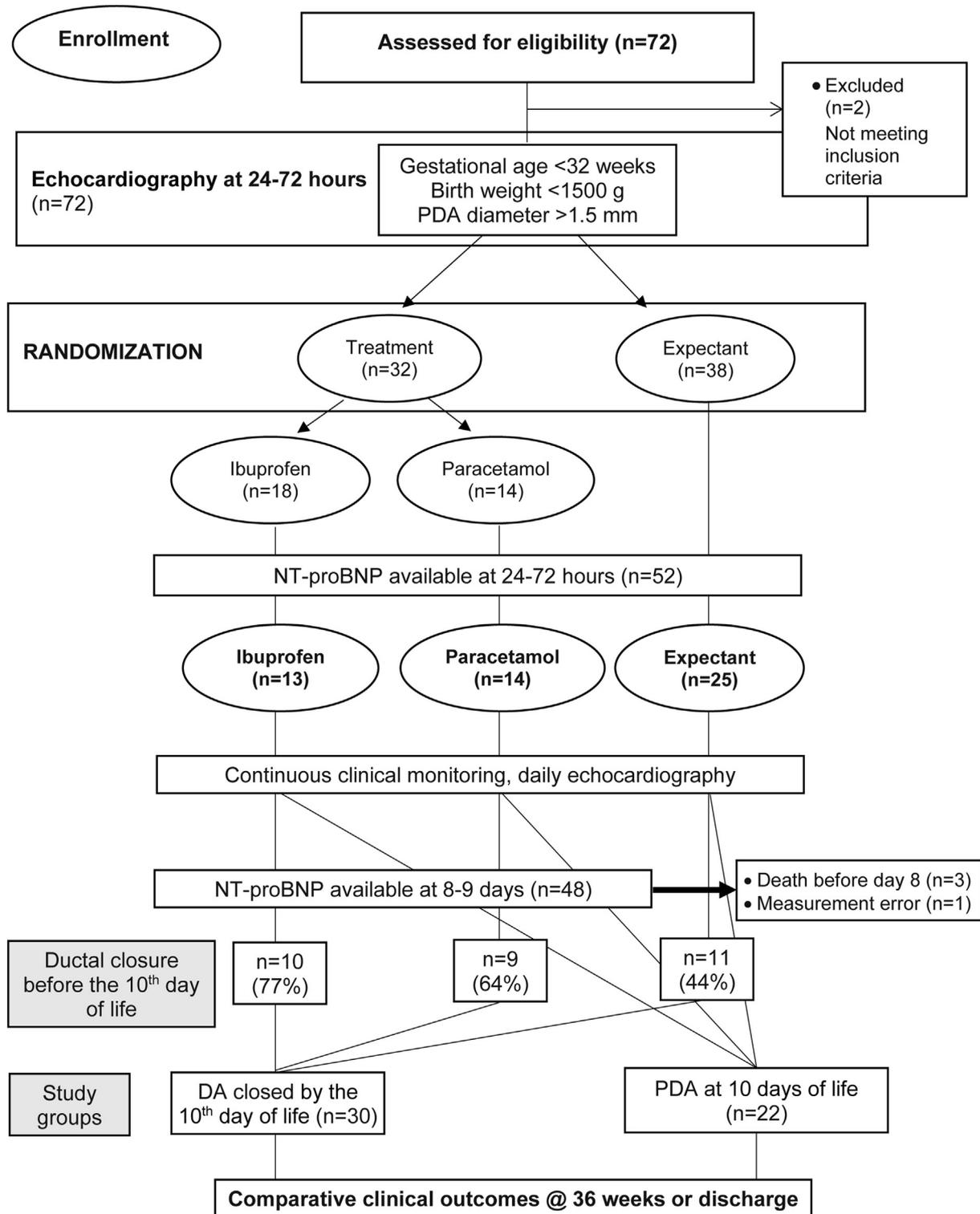


Fig. 1. Flow chart of study patients. DA = ductus arteriosus; NT-proBNP = N-terminal pro-brain natriuretic peptide; PDA = patent ductus arteriosus.

The study was performed in accordance with the principles stated in the Declaration of Helsinki. The local ethics committee approved the study protocol. Informed consent was obtained from parents of all patients involved in the study.

## 2.2. Clinical outcomes

The study groups were compared for major morbidity and mortality.

### 2.3. Measurement of serum concentrations of NT-proBNP

According to the study protocol, the blood samples for NT-ProBNP were drawn within 12 hours of echocardiographic evaluation. The blood samples were collected twice: within the first 24-72 hours of life (expectant group), and before the administration of ibuprofen/paracetamol (treatment group), and at the eighth or ninth day of life if the expectant management was used (expectant group) and after the end of the second course of the treatment (treatment group). The median [IQR] age of the first and repeated blood sampling were two [1-2] and eight [8-9] days, respectively. After each blood collection, serum was immediately obtained, frozen, and stored at minus 25°C. Serum NT-proBNP concentrations were measured using electrochemiluminescence immunoassay technique (Elecsys proBNP II test; Roche Diagnostics, Germany) according to the manufacturer's recommendations. Available measurement limits were 5-35,000 pg/mL.

### 2.4. Echocardiographic measurements

All patients underwent planned daily echocardiographic study within the first 10 days after birth, with a follow-up examination at 28 days of life and postmenstrual age of 36 weeks and/or discharge (whatever came first). Echocardiographic examination was performed using a Samsung Medison SonoAce X8 ultrasound machine (South Korea).

Ductal significance was determined by a ductal diameter >1.5 mm with unrestricted ductal left-to-right shunting ('pulsatile pattern'): end-diastolic flow velocity <50% of peak flow velocity, end-diastolic flow velocity >0.3 m/s, and/or the ratio of the left atrial to aortic root diameter (LA/Ao) > 1.5 and/or retrograde diastolic blood flow in descending aorta. At least one of the following signs, such as deterioration of the respiratory status with the requirement for invasive ventilation, increase in oxygen dependency, inability to wean from respiratory support, systemic hypotension, or congestive heart failure had to be present to confirm ductal significance [20-21].

### 2.5. Clinical data and monitoring

Standard protocols of respiratory support, disease management, and nutrition, as well as routine vital signs monitoring, were applied to all newborns.

### 2.6. Statistical analysis

Receiver operating characteristic (ROC) curves were generated to assess the predictive value of serum NT-proBNP concentrations for early DA closure. The area under the curve was determined, and corresponding sensitivity and specificity of different NT-proBNP values depending on the management of PDA were calculated.

Standard methods of descriptive, comparative, correlation, and logistic regression analysis using the  $\chi^2$ , Mann-Whitney, and Wilcoxon criteria, as well as adjusted odds ratios (aOR), were used in the study. Nonparametric data are presented as a median [IQR]. Correlation between nonparametric variables was assessed with Spearman's rank correlation coefficient ( $r_s$ ). All values were considered significant if  $p < 0.05$ .

## 3. Results

### 3.1. Comparative clinical characteristic of the groups

In the first ten days of life, DA closure occurred in 19 (70%) treated infants, and in 11 (44%) infants managed expectantly ( $p = 0.054$ ). By the tenth day of life, DA was closed in 30 (58%) infants (19 of them [63%] were treated and 11 [37%] – managed expectantly), but in 22 (42%) newborns (8 of them [36%] were treated and 14 [64%] – managed expectantly) it remained patent. At the time of discharge, DA was closed or became hemodynamically insignificant in all infants.

The study groups were not different in birth weight and gender. However, infants with PDA at ten days of life had significantly lower GA. The clinical characteristics of the groups are summarized in [Table 1](#).

The median size of PDA was not different between the groups. Nevertheless, in the first 72 hours of life, hsPDA was significantly more often detected in newborns with persistent PDA. The percentage of infants who received pharmacological treatment was significantly higher in the group with early DA closure, but the differences were not statistically significant. Infants with persistent PDA were more likely to require the second course of treatment and were almost three times older at primary DA closure. Of note, primary DA closure in these babies was an uncommon event during the first ten days of life. There were no statistically significant differences between groups in the frequency of re-opening and closing of DA at the time of discharge ([Table 2](#)).

Table 1. Comparative perinatal data of the patients.

Characteristics	Early ductal closure (n = 30)	Persistent PDA (n = 22)	p
Gestational age, weeks	29.5 (27-31) <sup>1</sup>	27.5 (25-28)	0.004
30-31 <sup>6/7</sup>	15 (50) <sup>2</sup>	1 (5)	0.002
28-29 <sup>6/7</sup>	6 (20)	10 (45)	
26-27 <sup>6/7</sup>	7 (23)	5 (23)	
23-25 <sup>6/7</sup>	2 (7)	6 (27)	
Birth weight, g	1075 (860-1350)	945 (740-1200)	NS
Male	12 (40)	14 (64)	NS
Small for gestational age	5 (17)	0	0.044
Preterm rupture of the membranes	7 (23)	4 (18)	NS
Clinical chorioamnionitis or fever >38° C during labor	2 (7)	2 (9)	NS
Antenatal steroids	22 (73)	14 (64)	NS
Cesarean section	15 (50)	7 (32)	NS
Apgar score at the 1 <sup>st</sup> min	6 (5-6)	4 (4-5)	0.006
Apgar score at the 5 <sup>th</sup> min	6 (6-7)	5 (5-6)	0.007
Mask ventilation after birth	5 (17)	2 (9)	NS
Intubation and ventilation after birth	16 (53)	19 (86)	0.012
Surfactant therapy	23 (77)	20 (91)	NS

Notes: 1 – median (interquartile range); 2 – number of cases (%). PDA: patent ductus arteriosus.

Table 2. Comparative ductus characteristics.

	Early ductal closure (n = 30)	Persistent PDA (n = 22)	p
Age at the time of PDA was diagnosed, days	2 (1-2) <sup>1</sup>	2 (1-2)	NS
The median size of PDA in the first 72 hours of life, mm	2.5 (2-3)	2.5 (2-3)	NS
hsPDA in the first 72 hours of life	8 (27) <sup>2</sup>	14 (64)	0.008
Pharmacological treatment	19 (63)	8 (36)	NS
Administration of ibuprofen	10 (33)	3 (14)	NS
Administration of paracetamol	9 (30)	5 (23)	NS
Two courses of treatment	1 (3)	8 (36)	0.00001
Primary DA closure	30 (100)	15 (68)	0.001
Age at the time of primary DA closure, days	5 (5-7)	16 (12-36)	0.000
Reopening of DA	7 (24)	1 (8)	NS
DA closed at the time of discharge	24 (86)	14 (82)	NS

Notes: 1 – median (interquartile range); 2 – number of cases (%). DA: ductus arteriosus; hsPDA: hemodynamically significant patent ductus arteriosus; PDA: patent ductus arteriosus.

There were no statistically significant differences between the groups in the incidence of major complications associated with preterm birth, survival without BPD, length of the hospital stay, or mortality (Table 3). No significant differences between systemic C-reactive protein (CRP) concentrations were found either at 2-3 days (3.4 [1.6-7.4] mg/l in newborns with early ductal closure and 6.1 [1.5-14.1] mg/l – in infants with PDA at 10 days of

life), or at 8-10 days (1.2 [0.7-2] mg/l and 1.6 [0.7-3.1] mg/l, respectively).

### 3.2. Serum NT-proBNP values depending on the ductus patency at the age of 10 days

Both median NT-proBNP values were significantly higher in newborns with persistent PDA. By the eighth day, the NT-proBNP concentrations have

Table 3. Comparative morbidity and mortality in the groups.

Diseases	Early ductal closure (n = 30)	Persistent PDA (n = 22)	p
Severe respiratory distress syndrome	3 (10) <sup>1</sup>	6 (27)	NS
Pneumonia	27 (90)	22 (100)	NS
Bronchopulmonary dysplasia	9 (30)	10 (45)	NS
Early onset sepsis	8 (27)	10 (45)	NS
Late onset sepsis	3 (10)	2 (9)	NS
Necrotizing enterocolitis	1 (3)	2 (9)	NS
IVH	10 (33)	9 (41)	NS
Severe IVH (3-4 grade)	3 (10)	5 (23)	NS
Death	2 (7)	5 (23)	NS
Age at the time of death, days	8.5 (7.2-9.8) <sup>2</sup>	8.1 (7.9-15)	NS
Length of hospital stay, days	64 (45-87)	69.5 (29-81)	NS

Notes: 1 – number of cases (%); 2 – median (interquartile range). IVH: intraventricular hemorrhage; PDA: patent ductus arteriosus.

Table 4. Comparative serum NT-proBNP concentrations in the groups.

Indicators	Ductal closure within 10 days of life (n = 30)	PDA by the 10 <sup>th</sup> day of life (n = 22)	p
NT-proBNP level in the first 24-72 hours of life, pg/ml	10262.5 (3947-16868)	20648.5 (6656-35000)	0.014
NT-proBNP level for 8-9 days of life, pg/ml	1610 (1144-2035) <sup>1</sup>	3995 (2701-8345) <sup>2</sup>	0.000

Notes: the median is indicated (interquartile range); 1 - the dynamics of the indicator is statistically significant ( $p < 0.001$ ); 2 - the dynamics of the indicator is statistically significant ( $p < 0.01$ ). NT-proBNP: N-terminal pro-brain natriuretic peptide; PDA: patent ductus arteriosus.

significantly decreased in all infants but remained considerably higher in newborns with persistent PDA. The decline happened sooner in infants with early DA closure, but this was not significant (Table 4). At the same time, the results of both NT-proBNP measurements did not differ depending on the pharmacological treatment received by the newborns.

Serum NT-proBNP concentrations on day two were significantly higher in newborns with a lower GA ( $r_s = -0.37$ ,  $p = 0.008$ ). At the same time, no significant correlation was found between NT-proBNP levels at this age and birth weight ( $r_s = -0.96$ ,  $p = 0.498$ ).

NT-proBNP levels were higher in newborns with higher systemic CRP concentrations on days two ( $r_s = 0.35$ ,  $p = 0.01$ ) and eight ( $r_s = 0.36$ ,  $p = 0.014$ ), and were associated with early onset sepsis ( $r_s = 0.29$ ,  $p = 0.036$ ) on day two, and with late onset sepsis on day eight ( $r_s = 0.3$ ,  $p = 0.036$ ).

Based on the area under the ROC curve (AUC = 0.63, 95% confidence interval (CI) 0.41–0.85,  $p = 0.274$ ), no NT-proBNP value on the second or third day of life could reliably predict early DA closure in infants who were managed expectantly. However, serum NT-proBNP levels at this age were predictive of early DA closure among the treated babies (AUC = 0.81, 95% CI 0.58–1.03,  $p = 0.014$ ) (Fig. 2).

Serum NT-proBNP concentrations  $\leq 23,800$  pg/ml in very preterm infants with PDA diameter  $>1.5$  mm at day two, had 95% sensitivity and 75% specificity to confirm the possibility of DA closure within the first 10 days of life in response to specific pharmacological treatment. According to the results of multivariate logistic regression analysis, that included the most important variables by which the groups differed, exceeding this cut-off NT-proBNP values identified almost zero odds of DA closure within the first 10 days of life (aOR = 0.05, 95% CI 0.007-0.41;  $p = 0.005$ ) despite the pharmacological treatment. Instead, greater GA and specific treatment significantly and independently increased such odds (aOR = 1.54, 95% CI 1.07-2.2,  $p = 0.02$  and aOR = 6.61, 95% CI 1.31-33.29,  $p = 0.02$ , respectively) in all patients involved in the study.

#### 4. Discussion

In this prospective study, we found that serum NT-proBNP concentration in newborns with GA  $<32$  weeks and birth weight  $<1500$  g at the age of 24-72 h could reliably predict DA closure in treated infants. However, serum NT-proBNP concentration had insufficient prognostic value to predict early spontaneous DA closure in infants who were managed expectantly. Unlike some other authors, we have failed to identify a cut-off baseline NT-

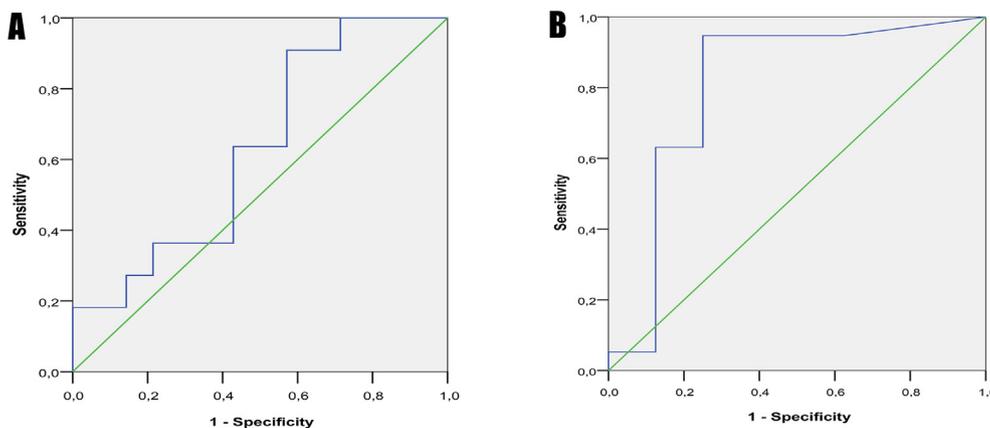


Fig. 2. ROC-curves describing N-terminal pro-brain natriuretic peptide cut-off values predicting PDA closure within the first 10 days of life in very preterm infants (A – infants managed expectantly; B – treated infants). PDA = patent ductus arteriosus.

proBNP value to predict early spontaneous DA closure in very preterm infants with PDA diameter >1.5 mm who were not treated [22,23]. This difference could be explained by the fact that in our study, for the first time the appropriate predictive value of serum NT-proBNP concentrations was evaluated in a randomized group of infants who were managed expectantly. At the same time, serum NT-proBNP concentrations >23,800 pg/ml on the second or third day of life had 95% sensitivity and 75% specificity in predicting the ineffectiveness of pharmacological treatment within the first 10 days of life. Therefore, high levels of serum NT-proBNP do not allow determining infants that need pharmacological treatment. A similar conclusion was made by Martinovici et al. [23] who showed that serum NT-proBNP level below the cutoff of 10,000 pg/ml on the second day of life was associated (89% sensitivity and 100% specificity) with spontaneous DA closure within the first week of life. Yet, any value above this threshold, as a single marker, could not identify neonates who would benefit from targeted PDA treatment [23].

According to our results, DA was closed significantly more often in newborns with higher GA and in infants small for GA. At the same time, DA remained persistently patent in the majority of infants that had hsPDA in the first 72 hours of life. During the first ten days of life, DA closed in 19 (70%) treated babies and in 11 (44%) infants who were managed expectantly, but differences between the groups were not significant. However, significantly more newborns with persistent PDA required the second course of pharmacological treatment, as it met the treatment criteria.

Our results confirmed the findings of Semberova et al. [24], that in infants with lower GA and birth weight spontaneous DA closure occurred relatively later and less frequently, and, accordingly, these infants were more compromised after birth than the more mature and larger newborns. Previous studies also found no statistical differences in the incidence of NEC, BPD, BPD or death, and mortality between the groups with early and late DA closure. Therefore, it could not be stated that DA closure within the first 10 days of life reduced the incidence of neonatal morbidity [5,6,24].

Our study for the first time demonstrated that serum NT-proBNP concentrations measured on the second-third day of life could predict the effectiveness of early PDA treatment with ibuprofen or paracetamol in very preterm infants. Hsu et al. [25] in the smaller prospective study showed that plasma BNP levels <1,805 pg/ml had high sensitivity and specificity (88% and 87%, respectively) in predicting

PDA closure after indomethacin treatment. Ding et al. [26] described the positive effect of ibuprofen treatment on the dynamics of NT-proBNP concentrations, linking the therapeutic effect of ibuprofen to this outcome. At the same time, Oh et al. [27] have failed to determine a cut-off value for BNP levels that could accurately predict the response to ibuprofen treatment in preterm infants with hsPDA. Thus, the possibility of using serum NT-proBNP concentrations in the first days of life to predict the effectiveness of PDA treatment in very preterm infants remains insufficiently studied and requires further research.

Serum NT-proBNP concentrations were significantly associated with systemic CRP levels and were higher in septic infants. Similar data were recently presented by Okur et al. [28], who also found a positive association between NT-proBNP and IL-6 plasma concentrations during the first five days of life. It is well established that cytokines are released during sepsis, and this can lead to myocardial dysfunction and increased NT-proBNP levels, [29,30] although the relevant mechanisms are insufficiently studied. The similarities between the groups in terms of the incidence of sepsis and systemic CRP concentrations do not allow linking the predominant increase of the NT-proBNP levels with the infectious process in any of the groups.

An additional factor that may affect serum NT-proBNP levels is the GA [31,32]. We found a significant negative correlation between serum NT-proBNP levels at days of life 2-3 and GA. These data confirmed the findings of Farombi-Oghuvbu et al. [32] on the inversely proportional effect of GA on the systemic NT-proBNP levels in the first days of life in preterm infants.

The advantages of our study are the prospective design and randomized treatment of very preterm infants with PDA diameter >1.5 mm started within the first 3 days of life, that allowed to eliminate the subjective factor in making management decisions, and objectively assess the predictive value of systemic NT-proBNP concentrations for early DA closure. For the first time, we obtained data on infants who were managed expectantly, despite the presence of hsPDA according to traditional definition [33].

Our study also has several limitations, primarily due to its non-blinded design, specific approach to treatment (early administration based only on the PDA size), the small number of patients to perform a subgroup analysis, depending on particular medication used. The number of extremely preterm infants was also small, thereby limiting the generalization of our results to more immature preterm infants.

The rationale for further research may be, on one hand, to confirm our results on the diagnostic value of systemic NT-proBNP concentrations in predicting the effectiveness of different approaches for medical PDA treatment involving more extremely preterm infants, and on the other hand, to obtain additional data suggesting against a significant association between serum NT-proBNP concentrations in the first days of life, and probability of early spontaneous DA closure in newborns, who were managed without pharmacological interventions.

## 5. Conclusions

Serum NT-proBNP concentrations in very preterm infants with PDA diameter of >1.5 mm at the age of 24–48 h could not predict spontaneous DA closure in the first 10 days of life but were useful for the prediction of efficacy of early PDA treatment with ibuprofen/paracetamol. Serum NT-proBNP levels  $\leq 23,800$  pg/ml could reliably predict early DA closure in treated newborns. The NT-proBNP concentrations above this threshold were independently significant predictors of PDA persistency beyond 10 days of life, despite the use of pharmacological treatment.

## Author contributions

Conception and design of Study: Solomiia Potsiurko, Dmytro Dobryansky. Literature review: Solomiia Potsiurko, Dmytro Dobryansky, Lesya Sekretar. Acquisition of data: Solomiia Potsiurko, Dmytro Dobryansky, Lesya Sekretar. Analysis and interpretation of data: Solomiia Potsiurko, Dmytro Dobryansky, Lesya Sekretar. Research investigation and analysis: Solomiia Potsiurko, Dmytro Dobryansky, Lesya Sekretar. Data collection: Solomiia Potsiurko, Lesya Sekretar. Drafting of manuscript: Solomiia Potsiurko, Dmytro Dobryansky, Lesya Sekretar. Revising and editing the manuscript critically for important intellectual contents: Solomiia Potsiurko, Dmytro Dobryansky, Lesya Sekretar. Supervision of the research: Dmytro Dobryansky. Research coordination and management: Dmytro Dobryansky.

## Conflict of interest

None declared.

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