The chance of spontaneous patent ductus arteriosus closure in preterm infants born before 32 weeks of gestation is high and continues to increase until 5 years of follow-up

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ORIGINAL ARTICLE

The chance of spontaneous patent ductus arteriosus closure in preterm infants born before 32 weeks of gestation is high and continues to increase until 5 years of follow-up

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Abstract

Aim: The primary aim was to estimate premature infants' spontaneous patent ductus arteriosus closure rate. Secondly, to identify criteria associated with the chance of spontaneous closure.

Methods: We performed a retrospective cohort study of 167 infants born before 32 weeks of gestation and diagnosed with a patent ductus arteriosus between 1 January 2008 and 31 December 2017. The spontaneous patent ductus arteriosus closure event rate was evaluated using the Kaplan–Meier estimator.

Results: The spontaneous closure rate within the first year of life was 66% (95% CI 58%–73%), increasing to 80% (95% CI 72%–86%) five years after birth. When including both spontaneous closure and closure following treatment, 96% (95% CI 86%–100%) closed within 5 years after birth. The chance of spontaneous closure was reduced in the case of a large patent ductus arteriosus: OR 0.16 (95% CI 0.05–0.52), left atrial enlargement: OR 0.16 (95% CI 0.05–0.51), and pulmonary hypertension: OR 0.23 (95% CI 0.07–0.74).

Conclusion: The chance of spontaneous closure in premature infants born between 23 and 32 weeks of gestation was high, and the incidence continued increasing until 5 years of follow-up.

KEYWORDS
neonatology, patent ductus arteriosus, preterm

Abbreviations: ASD, atrial septal defect; BPD, bronchopulmonary dysplasia; CI, confidence interval; COX, cyclooxygenase; CPAP, continuous positive airway pressure; GA, gestational age; IQR, interquartile range; IUGR, intrauterine growth restriction; IVH, intraventricular haemorrhage; LA/Ao, Left atrial/aortic root ratio; MeSH terms, Medical Subject Headings; NEC, necrotising enterocolitis; NSAID, non-steroid anti-inflammatory drug; OR, odds ratio; PDA, patent ductus arteriosus; PFO, patent foramen ovale; PICO, population, intervention, comparison, outcome; PPROM, preterm premature rupture of membranes; RDS, respiratory distress syndrome; VSD, ventricular septal defect.

1 | INTRODUCTION

Patent ductus arteriosus (PDA), the most commonly diagnosed cardiovascular condition in preterm infants, is associated with an eight-fold increase in mortality[1] and multiple, harmful longer-term outcomes including bronchopulmonary dysplasia (BPD), necrotising enterocolitis (NEC), intraventricular haemorrhage (IVH), and death.[1–4] The ductus, an essential component of foetal circulation, normally closes within the first days of life.[5] However, in preterm infants, closure of the ductus arteriosus is frequently delayed or fails to eventuate due to generalised immature structures and biochemical oxygen sensing mechanisms.[6] The prevalence of PDA in premature infants has been found to be between 42 and 68%, however gestational age (GA) varied between studies.[7–9] The incidence of PDA is inversely proportional to GA and birth weight,[10] and the highest incidence is reported in preterm infants born before 28 weeks of gestation.[9] No validated criteria currently exist to permit early identification of those infants with increased probabilities of persistent PDA and PDA-associated harm.

Currently, there is no consensus on the optimal treatment approach, and PDA treatment rates seem to vary four-fold among European regions.[11] Over the years, various treatment strategies have been suggested, including pharmaceutical treatment with cyclooxygenase (COX) inhibitors, surgical ligation, and catheter-based procedures.[12] Despite no golden standard, pharmacotherapy with COX inhibitors continues to be the first-line choice[13] alongside supportive therapy, including respiratory support, fluid restriction, and diuretics.[12] Yet, there is no evidence of improved outcomes after PDA treatment, presumably due to the high spontaneous closure rate.[11,14] As a result, medical and surgical treatment has decreased during the past years as watchful waiting has become more widespread.[8,15] Up to 22% of infants are discharged from the hospital with a PDA[7,16] which makes it crucial to comprehend the long-term outcomes in these patients. In selected cohorts, the spontaneous closure rate after hospital discharge has been evaluated, with an incidence of up to 92%.[7,16–18] Only one study performed follow-up until the closure of the PDA was obtained.[16] No other studies exist with a minimum follow-up above 36 months.[7,17,18] Nevertheless, the evidence concerning spontaneous PDA closure rate in preterm infants discharged with a PDA is sparse.[9,19]

The primary aim of this study was to estimate the spontaneous PDA closure rate in premature infants born before 32 weeks of gestation. The secondary aim was to identify criteria associated with the chance of spontaneous closure.

Key Notes

- To estimate premature infants' spontaneous patent ductus arteriosus closure rate.
- The chance of spontaneous closure was high, and the incidence continued increasing 5 years after birth.
- There was a reduced chance of spontaneous closure in the case of a large-sized PDA, left atrial enlargement, and pulmonary hypertension, so these findings may be reasonable to consider when deciding on the PDA treatment approach and determining the frequency and time of follow-up.

2 | METHODS

This retrospective cohort study included consecutive cases of infants born before 32 weeks of gestation. They were diagnosed between 1 Jan 2008 and 31 Dec 2017 at Aalborg University Hospital, Denmark. All infants who had an echocardiographic or autopsy-verified PDA were eligible for inclusion. We excluded infants who were not born in the North Denmark Region.

Data were collected by a review of medical charts as we collected, information about maternal, perinatal, and neonatal characteristics as well as PDA characteristics, clinical findings, treatment, and PDA status at discharge. In addition, the date of admission, date of discharge, last date of follow-up, date of death, and date of identified ductal closure were registered.

A complete echocardiographic assessment was performed when clinically indicated. The following echocardiographic findings were noted: diameters of the left atrium, the aorta, the left ventricle (measured on the M-mode on the short axis view), and the ductus arteriosus (measured on the suprasternal view of the aorta at its narrowest part identified via colour Doppler and measured on 2D). Furthermore, flow patterns and velocities in the duct, the aorta, and the pulmonary artery were noted. Left atrial/aortic root ratio (LA/Ao) was calculated and eventually left atrial enlargement (LA/Ao > 1.3) and left ventricular enlargement (defined by values higher than those expected for GA and weight)[20,21] were determined. The presence of pulmonary hypertension (pulmonary pressure > 25 mmHg calculated via continuous Doppler of the tricuspid regurgitation), reverse flow in the diastole in the descending aorta, and other congenital heart defects were registered.

The echocardiographic classification of the PDA size was divided into three groups: small (<1.5 mm and no dilatation of the left cavities, normal LA/Ao ≤ 1.3), moderate (1.5–3.0 mm, and light dilatation of the left cavities, LA/Ao between 1.3 and 1.5), and large (>3.0 mm and severe dilatation of left cavities, LA/Ao > 1.5 and reverse flow in the diastole in the descending aorta). In some cases, the ductus was evaluated between two groups (due to difficulties measuring the diameter) and therefore categorised into an intermediate group: small-moderate or moderate-large. The PDA registered in the study is the largest one visualised and measured among all echocardiographic assessments, independent of size change during the follow-up period.

Each infant underwent continuous echocardiographic follow-up until verified closure, or the PDA was assessed as clinically insignificant. Usually, echocardiography was performed every 6 months or more if clinically indicated.

2.1 | Statistical analysis

The continuous variables were non-normally distributed, evaluated by QQ-plots and histograms, and reported with median and interquartile range (IQR). Comparisons were made using the Mann–Whitney U test for the continuous variables and Fisher's exact test for the dichotomous variables. The spontaneous closure rate and the total rate of PDA closure were analysed using Kaplan–Meier estimation, including 1, 2, and 5-years specific closure rates with a 95% confidence interval (CI). Univariate and multivariate logistic regression identified clinical features associated with spontaneous closure. We used STATA V.17.0 (Stata MP) for the statistical analysis, and all tests were performed under a two-sided significance level of 0.05. The study was approved by the Danish Data Protection Agency (ID number: 2021-182).

2.2 | Literature

The PICO (population, intervention, comparison, outcome) method was used to identify Medical Subject Headings (MeSH terms) and topic-specific search words. Subsequently, an evidence-based literature search was carried out in PubMed and Embase. After the removal of duplicates 197 results appeared, these were briefly reviewed and sorted by relevance based on title and abstract.

3 | RESULTS

We identified 648 infants born before 32 weeks of gestation (GA 23 + 3 – 31 + 6), admitted to a hospital in the North Denmark Region between 1 Jan 2008 and 31 Dec 2017. Of all infants, 182/648 (28%) had an echocardiographic or autopsy-verified PDA. Fifteen infants not born in the North Denmark Region were excluded (Figure 1). The 167 infants included for analysis had a GA between 23 + 5 – 31 + 6.

Among the 167 infants, PDA closed without treatment in 115/167 (69%), and 27/167 (16%) closed after treatment at some point during the follow-up period 5 years after birth. In 23/167 (14%) the PDA outcome was unresolved due to either missing data 5/167 (3%), or death 17/167 (10%), Figure 1. Of the 17 infants who died, eight were reported with a large-sized PDA, three had a moderate-sized, two had a small-sized, and in four cases the PDA size was unknown. We did not report the cause of death. Spontaneous PDA closure occurred in 115/167 (69%), hereof 48/167 (29%) prior to discharge, and 67/167 (40%) after discharge. In 27/167 (16%) of the cohort the PDA did not close spontaneously, but due to ibuprofen treatment (4%), surgical ligation (5%), or transcatheter PDA closure (7%). Further, 3/167 (2%) are in continuous PDA follow-up.

The clinical characteristics of the total cohort are listed in Table 1. The median GA was 27 + 6 weeks (IQR 26 + 2;29 + 5) and the median birth weight was 1073 g (IQR 797;1301). All infants received continuous positive airway pressure (CPAP)/high flow treatment, except seven infants who died during mechanical ventilation treatment. Of

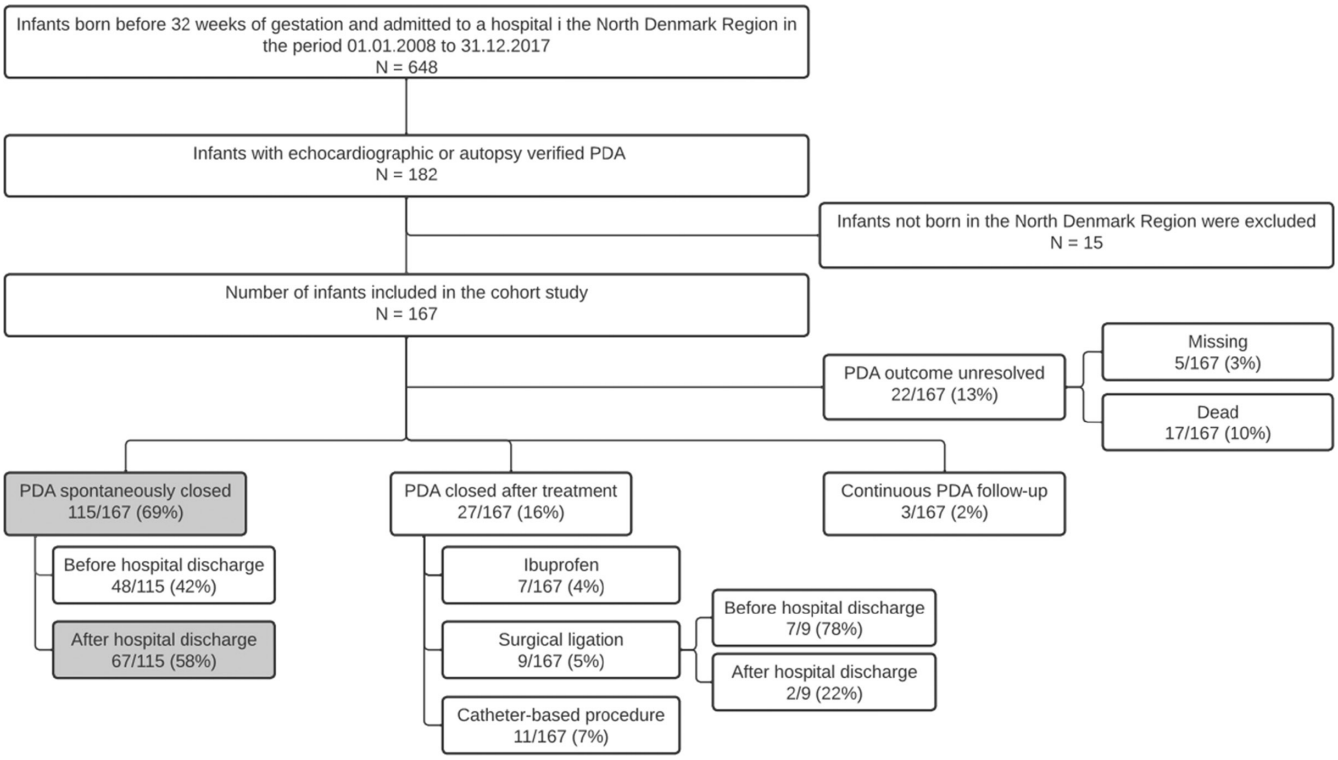

FIGURE 1 Flowchart of the study population and the PDA outcome and treatment distribution before and after hospital discharge in the total cohort of 167 infants. PDA, patent ductus arteriosus

TABLE 1 Clinical characteristics of the total cohort

	Number of infants *N* = 167 *n* (%)
Neonatal characteristics	
Male	97 (58%)
Days of admission, median (IQR)	76 (55;101), *n* = 164
GA (weeks), median (IQR)	27 + 6 (26 + 2;29 + 5)
Birth weight (gram), median (IQR)	1073 (797;1301), *n* = 166
Apgar score 5 min., median (IQR)	9 (7;10), *n* = 156
IUGR	20 (12%)
Perinatal and maternal characteristics	
Maternal diabetes	4 (2%)
Maternal hypertension	11 (7%)
Preeclampsia	23 (14%)
Maternal infection	42 (25%), *n* = 166
PPROM	39 (23%)
Antenatal steroids[a]	106 (65%), *n* = 164
Spontaneous onset of labour	106 (64%), *n* = 165
Caesarean section	104 (62%)
CPAP/high flow treatment	160 (96%)
Oxygen	154 (92%)
Mechanical ventilation	89 (53%)
RDS	151 (90%)
Surfactant	115 (69%)
BPD	69 (41%)
Steroid treatment for BPD	27 (16%)
NEC	16 (10%)
Renal failure	16 (10%)
IVH	59 (35%)
Sepsis	107 (64%)

Note: *N* = 167 unless otherwise stated.

Abbreviations: BPD, bronchopulmonary dysplasia; CPAP, continuous positive airway pressure; GA, gestational age; IUGR, intrauterine growth restriction; IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; PDA, patent ductus arteriosus; PPROM, preterm premature rupture of membranes; RDS, respiratory distress syndrome.

[a]Administered >12 h before birth.

all infants, 154/167 (92%) required oxygen supplements, and 89/167 (53%) received mechanical ventilation. Respiratory distress syndrome (RDS) occurred in 151/167 (90%) infants and BPD in 69/167 (41%) (Table 1). 59/167 (35%) infants were reported with IVH, grades I and II being the most frequent, represented by 29/59 (49%) and 14/59 (24%), respectively. Grade III occurred in 9/59 (15%) and grade IV in 7/59 (12%).

The majority of the cohort was registered with PDA symptoms, most often in the form of saturation drop 164/167 (98%), trouble feeding 162/167 (97%), or heart murmur 150/167 (90%), Table 2. The PDA sizes were relatively equally represented among the infants; 32% small, 8% small-moderate, 26% moderate, 6% moderate-large, and 23% had a large. An atrial septal defect/patent foramen ovale (ASD/PFO) accompanied the PDA in 152/167 (91%) of the infants. Non-steroid anti-inflammatory drug (NSAID) was administered to 44/167 (26%), mainly as ibuprofen (98%) and one as indomethacin. However, only 38/43 (88%) completed the planned ibuprofen regime. At the time of discharge from the hospital, 84/140 (60%) still had a PDA (Table 2).

Infants discharged from the hospital with a PDA were divided into two groups based on the PDA outcome at the last follow-up: One group with spontaneous closure of the PDA 67/84 (80%) and a group of infants who had assisted closure of the PDA 16/84 (19%), Table 3. The assisted closure after hospital discharge included 2/16 (13%) who had performed surgical ligation and 11/16 (69%) who had performed a catheter-based procedure, corresponding to 2/167 (1%) and 11/167 (7%) of the total cohort. 3/16 (19%) infants continued follow-up.

No infants died after hospital discharge. The two groups did not differ regarding neonatal, perinatal, or maternal characteristics, including maternal risk factors, preterm premature rupture of membranes (PPROM), antenatal steroids, or birth complications. Neither did the occurrence of PDA symptoms or extent of respiratory support, steroid, or sepsis treatment. More than half of the infants received sepsis treatment in both groups, but there was no significant difference in the number of infants treated or the duration of sepsis treatment. Closure after treatment with NSAID was considered successful if the PDA closed within 48 h of the last dose administered. In total, 18/67 (27%) infants with a spontaneously closed PDA received treatment with NSAID. Nevertheless, a successful closure within 48 h after treatment never occurred.

In the comparison of the group with spontaneous closure ($n = 67$) versus the group who had assisted closure of the PDA ($n = 16$) after discharge, they did differ regarding PDA size and echocardiographic findings (Table 3). A small PDA was more frequent in the group with spontaneous closure 31/67 (46%) versus 1/16 (6%), $p < 0.001$. In contrast, a large PDA was less frequent in the group with spontaneous closure 9/67 (13%) versus 8/16 (50%), $p < 0.001$. Further, left atrial enlargement, ventricular enlargement, and pulmonary hypertension were more frequent in the group who had assisted PDA closure performed (Table 3).

There was no significant difference in morbidities associated with PDA (IVH, NEC, BPD, and renal failure) between the two groups discharged with a PDA. IVH was the most common complication in both groups, present in 21/67 (31%) infants with a spontaneously closed PDA and 7/16 (44%) infants with a PDA that needed assisted closure. In both groups, the majority of infants had an IVH grade I or II. Grade I was seen in 10/67 (15%) infants with a spontaneously closed PDA and 6/67 (9%) had a grade II. In the other group, 3/16 (19%) had a grade I and 4/16 (25%) a grade II. Only five infants with a spontaneously closed PDA had a severe (grade III or IV) IVH and no infants in the other group had an IVH higher than grade II. NEC was diagnosed in 6% of each group.

TABLE 2 PDA characteristics and treatment for the total cohort

	Number of infants $N = 167$ *n* (%)
PDA symptoms	
Saturation drop	164 (98%)
Trouble feeding	162 (97%)
Heart murmur	150 (90%)
Massive weight gain[a]	122 (73%)
Poor weight gain[b]	86 (52%)
Tachypnoea	85 (51%)
Fatigue	78 (47%)
Weight loss[c]	67 (40%)
Tachycardia	49 (29%)
Cyanosis	25 (15%)
PDA size	
Small PDA	54 (32%)
Small-moderate PDA	13 (8%)
Moderate PDA	44 (26%)
Moderate-large PDA	10 (6%)
Large PDA	39 (23%)
Echocardiographic findings	
Left atrial enlargement[d]	47 (28%)
Left ventricular enlargement[e]	42 (25%)
Pulmonary hypertension[f]	40 (24%)
ASD/PFO	152 (91%)
VSD	9 (5%)
PDA at discharge	84 (60%), $n = 140$
Treatment	
Fluid restriction	84 (50%)
Diuretics	51 (31%)
NSAID	44 (26%)
Completed second ibuprofen regime	4 (100%)
Surgical ligation	9 (5%)
Age at surgical ligation (days), median (IQR)	43 (37;73)
Catheter-based procedure	11 (7%)
Age at catheter-based procedure (days), median (IQR)	333 (288;501)
Spontaneously closed PDA	115 (69%)

Note: $N = 167$, unless otherwise stated.

Abbreviations: ASD, atrial septal defect; Large PDA, >3.0 mm and severe dilatation of left cavities, LA/Ao >1.5 and reverse flow in the diastole in the descending aorta; Moderate PDA, 1.5–3.0 mm and light dilatation of the left cavities, LA/Ao between 1.3 and 1.5; NSAID, non-steroid anti-inflammatory drug; PDA, patent ductus arteriosus; PFO, Patent foramen ovale; Small PDA, <1.5 mm and no dilatation of the left cavities, normal LA/Ao ≤1.3; VSD, ventricular septal defect.

[a]Defined as weight gain >40 g/day or clinical signs of oedema or congestive heart insufficiency.

[b]Defined as weight gain <20 g/day.

[c]Defined as weight loss of more than 10% within the first week of life or any weight loss after the first week of life.

[d]Defined as LA/Ao > 1.3.

[e]Defined by values higher than those expected for GA and weight.

[f]Defined as pulmonary pressure > 25 mmHg calculated via continuous Doppler of the tricuspid regurgitation.

Clinical features associated with spontaneous closure were further identified using logistic regression. The chance of spontaneous closure was reduced in the case of: (1) a large PDA: odds ratio (OR) 0.16 (95% CI 0.05–0.52), (2) left atrial enlargement: OR 0.16 (95% CI 0.05–0.51), and (3) pulmonary hypertension: OR 0.23 (95% CI 0.07–0.74). The multivariate logistic regression, including all three variables, revealed an OR of 0.21 (95% CI 0.06–0.78). Univariate logistic regression of the remaining relevant clinical features did not significantly affect the outcome (data not shown).

In a Kaplan–Meier curve, we evaluated the event rate of spontaneous PDA closure (Figure 2) for spontaneous PDA closure and the total PDA closure rate, including both spontaneous closure and closure following treatment. Within the first year of life, the chance of spontaneous PDA closure was 66% (95% CI 58%–73%), increasing to 72% (95% CI 65%–79%) within the second year. The chance of spontaneous closure within 2–5 years after birth was 80% (95% CI 72%–86%). Thus, the chance of spontaneous closure of a PDA still present at the age of 1 year was 14%. Since the Kaplan–Meier estimation corrects for follow-up time these estimates provide a more accurate probability of the chance of spontaneous closure compared to the overall number of spontaneously closed PDAs of 115/167 (69%) within the total follow-up period.

For the total cohort, the chance of PDA closure within the first year of life was 73% (95% CI 65%–81%). However, this chance increased to 83% (95% CI 75%–89%) within the second year of life, and to 96% (95% CI 86–100%) within the time from 2 to 5 years after birth.

4 | DISCUSSION

Conservative PDA treatment has become more widespread, and as a consequence, more infants are discharged from the hospital with a PDA.[7,8,15,16] Among these infants, multiple studies have reported high rates of spontaneous PDA closure, up to 92%.[7,16–18] The present study confirmed a high rate of spontaneous PDA closure, which continued increasing until five years of follow-up to 80%, emphasising the possibility of spontaneous ductal closure years after hospital discharge. Furthermore, a small but not insignificant number of infants needed assisted closure of the PDA after discharge, which indicates a need for close follow-up.

Of the 648 infants born before 32 weeks of gestation during the 10-year study period, 28% were diagnosed with a PDA. This is less than previous studies that report a PDA prevalence of 31%–68%.[7,9,16] This may be because systematically echocardiography was performed in previous studies, in contrast to our study in which echocardiography was performed only when clinically indicated.

The present study revealed spontaneous closure of 69% of all PDAs among premature infants born before 32 weeks of gestation. This is in accordance with a similar retrospective cohort study of 103 infants, in which 73% of PDAs present beyond 72 h after birth showed subsequent spontaneous closure.[9] Half of our cohort was discharged from the hospital with a PDA, and hereof 80% closed spontaneously within 5 years after birth. In comparison, other

TABLE 3 Comparison of the clinical characteristics and treatment among infants with and without spontaneous PDA closure after hospital discharge

	PDA spontaneously closed after hospital discharge ($N = 67$)	PDA not spontaneously closed after hospital discharge ($N = 16$)	
	n (%)	*n* (%)	*p*-value
Neonatal characteristics			
Male	44 (66%)	7 (44%)	0.15
Days of admission, median (IQR)	70.0 (55.0;90.0)	84.5 (51.2;100.0)	0.51
GA (weeks), median (IQR)	28 + 4 (26 + 6;30 + 1)	28 + 0 (26 + 1;30 + 5)	0.82
Birth weight (g), median (IQR)	1155.0 (895.0;1345.0)	1077.5 (738.2;1645.0)	0.96
Apgar score 5 min., median (IQR)	9.0 (8.0;10.0), $n = 64$	9.0 (8.0;10.0), $n = 13$	0.72
IUGR	9 (13%)	3 (19%)	0.69
CPAP/high flow treatment	67 (100%)	16 (100%)	-
Oxygen supplement	59 (88%)	15 (94%)	1.00
Mechanical ventilation	28 (42%)	10 (63%)	0.17
RDS	59 (88%)	15 (94%)	1.00
Surfactant	45 (67%)	11 (69%)	1.00
BPD	23 (34%)	7 (44%)	0.57
Steroid treatment for BPD	7 (10%)	3 (19%)	0.40
Sepsis	35 (52%)	11 (69%)	0.27
PDA size			
Small PDA	31 (46%)	1 (6%)	**0.00**
Small-moderate PDA	3 (5%)	2 (13%)	0.24
Medium PDA	17 (25%)	5 (31%)	0.75
Medium-large PDA	4 (6%)	0 (0%)	1.00
Large PDA	9 (13%)	8 (50%)	**0.00**
PDA reopened	1 (2%)	3 (19%)	**0.02**
Echocardiographic findings			
Left atrial enlargement[a]	14 (21%)	10 (63%)	**0.00**
Left ventricular enlargement[b]	13 (19%)	7 (44%)	0.05
Pulmonary hypertension[c]	10 (15%)	7 (44%)	**0.02**
ASD/PFO	63 (94%)	16 (100%)	1.00
VSD	3 (5%)	2 (13%)	0.24
Treatment			
Fluid restriction	29 (43%)	10 (63%)	0.26
Diuretics	12 (18%)	6 (38%)	0.10
NSAID	18 (27%)	4 (25%)	1.00
Completed second ibuprofen regime	1 (100%)	0 (0%)	–

Note: $N = 67$ in the group of infants with a spontaneously closed PDA after hospital discharge, unless otherwise stated. $N = 16$ in the group of infants with a not spontaneously closed PDA after hospital discharge, unless otherwise stated.

Abbreviations: ASD, atrial septal defect; BPD, bronchopulmonary dysplasia; CPAP, continuous positive airway pressure; GA, gestational age; IUGR, intrauterine growth restriction; Large PDA, >3.0 mm and severe dilatation of left cavities, LA/Ao > 1.5 and reverse flow in the diastole in the descending aorta; Moderate PDA, 1.5–3.0 mm and light dilatation of the left cavities, LA/Ao between 1.3 and 1.5; NSAID, non-steroid anti-inflammatory drug; PDA, patent ductus arteriosus; PFO, Patent foramen ovale; RDS, respiratory distress syndrome; Small PDA, <1.5 mm and no dilatation of the left cavities, normal LA/Ao ≤ 1.3; VSD, ventricular septal defect.

Bold indicates significant *p*-values.

[a]Defined as LA/Ao > 1.3.

[b]Defined by values higher than those expected for GA and weight.

[c]Defined as pulmonary pressure > 25 mmHg calculated via continuous Doppler of the tricuspid regurgitation.

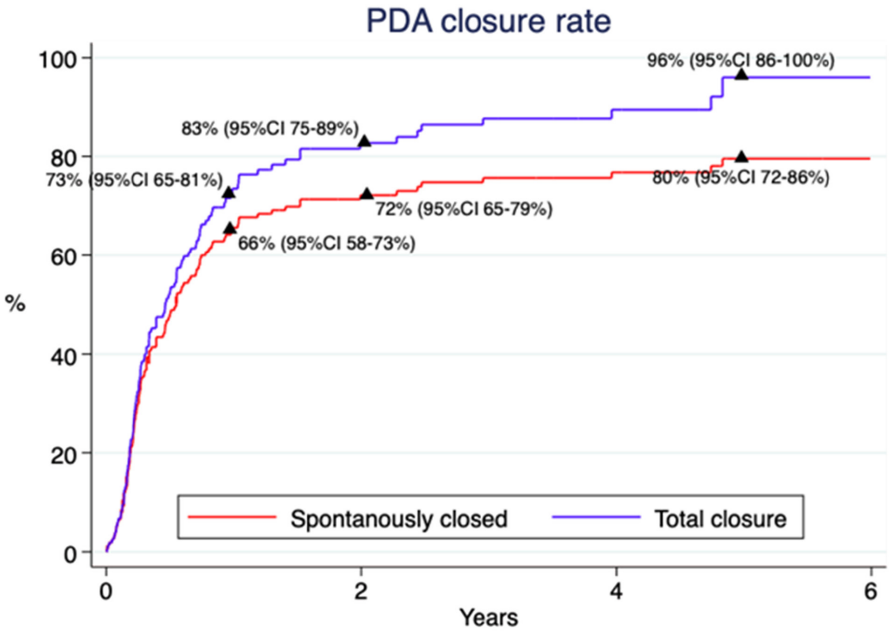

FIGURE 2 Kaplan–Meier curves illustrate the spontaneous PDA closure rate (red curve) and the total PDA closure rate (blue curve), including spontaneously closed PDAs and PDAs closed after treatment. Time is given in years after birth. PDA: patent ductus arteriosus. Kaplan–Meier estimations are corrected for follow-up time and are therefore different from the proportion of spontaneously closed PDAs shown in Table 2

studies have reported rates of spontaneous closure ranging from 58% to 92%.[7,16–18] The longer follow-up period in the present study may explain why we found a higher spontaneous closure rate after hospital discharge than Tolia et al., who had a follow-up period at 18 months and a spontaneous closure rate after hospital discharge at 58%.[17]

However, when comparing results from our study with the literature, it should be interpreted with caution. In our study, PDA sizes were relatively equally distributed between small, moderate, and large groups. In contrast, infants in multiple other studies were reported with either a small or moderate-sized PDA,[16,17] presumably resulting in favourable outcomes. It has been shown that cases with a larger PDA size are more prone to require assisted closure, either pharmacological or surgical, whereas minor PDAs are more likely to close spontaneously.[22] Despite differences in both PDA sizes and follow-up period, our cohort of infants was in agreement with other studies that report similar median GA and birth weight, hence making our findings comparable.[7,16–18]

The incidence of NEC in our study was 10% which is high compared to 2–8% in other premature infants.[23–25] In addition, 35% of our cohort was diagnosed with IVH, being in the upper range of the incidence of 12–34% among extremely premature infants born before 28 weeks of gestation.[26,27] However, the incidence of severe IVH was low in our cohort compared to literature reporting severe IVH present in 12–20%.[26,28] Though, it should be taken into consideration that the population in these studies is younger than ours. Both NEC and IVH are complications associated with PDA, which might explain the high prevalence in our study. However, we cannot establish the causality of this relationship due to the study design.

Previous studies have tried to identify factors at hospital discharge associated with the chance of spontaneous closure. Higher GA and birth weight was associated with an increased chance of spontaneous PDA closure.[7,17] In the present study, we did not find any difference in GA or birth weight for children with spontaneous closure versus those without. On the other hand, the following characteristics were associated with a decreased chance of spontaneous PDA closure: large-sized PDA, left atrial enlargement, and pulmonary hypertension. The association was less significant when combined in multivariate logistic regression, probably because the three variables were interdependent and occurred simultaneously.

Our results support the findings by Tolia et al.,[17] who reported moderate-sized PDA and left ventricular enlargement to be common among infants who received assisted PDA closure. Therefore, we recommend special attention and closer follow-up in the subgroup with large-sized PDA, pulmonary hypertension, and left ventricular enlargement.

This is in accordance with a published practice guideline by the American Heart Association[29] regarding PDA catheterisation in non-premature infants. The recommendations imply ductal closure in cases with a moderate or large PDA with a left-to-right shunt, resulting in congestive heart failure, failure to thrive, pulmonary over circulation, or an enlarged left atrium or ventricle.[29] The proportion of infants requiring assisted closure in our study corresponds to previous findings.[7,16–18] The catheter-based procedure is the most frequent surgical treatment in infants with a median GA of 27 weeks.[17] Notably, the rate of assisted closure seems to be more or less consistent, despite the changes towards a more conservative approach over the past decades.

4.1 | Strength and weaknesses

A substantial strength of this study was the large non-selected cohort of 167 infants with only five infants lost to follow-up. In addition, all Danish citizens are registered with a personal identification

number, which ensures the inclusion of all premature infants born in the study period and allows for the possibility of a complete follow-up. Furthermore, the Danish population has free and equal access to health care in Denmark, which minimises the risk of socioeconomic status influencing the inclusion or follow-up of the infants.

Due to this study's retrospective design, the results must be interpreted cautiously and have several limitations. The follow-up program for infants discharged with a PDA was not standardised, which may obscure the time of PDA closure since it may be random if the echocardiographic control was performed at a certain time. The echocardiography was not performed routinely on premature infants, presumably underestimating PDA incidence. Furthermore, there is a risk of interobserver variability as multiple doctors have performed the echocardiographic assessments. In addition, echocardiography in preterm infants is affected by the child's condition. Parameters such as apnoea, bradycardia, arterial hypotension, or change of skin colour during the examination may change the hemodynamic measurements and affect the accuracy of the assessments. The lack of accuracy has been pointed out in other studies.[30] However, this is a single-centre cohort study performed in a consecutive period, which minimises the risk of coincidences and interobserver variability.

Despite the large cohort of infants included in this study, the comparison analysis between the two groups discharged with a PDA was made on small samples, which could increase the risk of bias.

We did not register hospital readmission of the infants discharged with a PDA. Therefore, it is not possible to determine if any post-discharge condition could have influenced the course of PDA closure. However, a previous study found no significant difference in hospital readmission among infants discharged with a PDA.[17]

5 | CONCLUSION

The chance of spontaneous PDA closure in premature infants born between 23 and 32 weeks of gestation was high and continued increasing until 5 years of follow-up to 80%, emphasising the possibility of spontaneous ductal closure years after hospital discharge. Secondly, we found a reduced chance of spontaneous closure in the case of a large-sized PDA, left atrial enlargement, and pulmonary hypertension. These findings may be reasonable to consider when deciding which PDAs that safely can be treated conservatively and which require more aggressive treatment and determining the frequency and time of follow-up.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

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