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Outcomes for Infants Born in Perinatal Centers Performing Fewer Surgical Ligations for Patent Ductus Arteriosus: A Swiss Population-Based Study

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Abstract: Objective To assess patent ductus arteriosus treatment variation between Swiss perinatal centers and to determine its effect on outcome in a population-based setting. Study design This was a retrospective cohort study of infants born less than 28 weeks of gestation between 2012 and 2017. Outcomes between surgically ligated and pharmacologically treated infants as well as infants born in centers performing 10% ligation ("low" group) and >10% ("high" group) were compared using logistic regression and 1:1 propensity score matching. Matching was based on case-mix and preligation confounders: intraventricular hemorrhages grades 3-4, necrotizing enterocolitis, sepsis, and 28 days' oxygen supply. Results Of 1389 infants, 722 (52%) had pharmacologic treatment and 156 (11.2%) received surgical ligation. Compared with infants who received pharmacologic treatment, ligated infants had greater odds for major morbidities (OR 2.09, 95% CI 1.44-3.04) and 2-year neurodevelopmental impairment (OR 1.81, 95% CI 1.15-2.84). Mortality was comparable after restricting the cohort to infants surviving at least until day 10 to avoid survival bias. In the "low" group, 34 (4.9%) of 696 infants were ligated compared with 122 (17.6%) of 693 infants in the "high" group. Infants in the "high" group had greater odds for major morbidities (OR 1.49, 95% CI 1.11-2.0). Conclusions Our analysis identified a burden on infants receiving surgical ligation vs pharmacologic treatment in a population-based setting where there was no agreed-on common procedure. These results may guide a revision of patent ductus arteriosus treatment practice in Switzerland.

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Outcomes for Infants Born in Perinatal Centers Performing Fewer Surgical Ligations for Patent Ductus Arteriosus: A Swiss Population-Based Study

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Objective To assess patent ductus arteriosus treatment variation between Swiss perinatal centers and to determine its effect on outcome in a population-based setting.

Study design This was a retrospective cohort study of infants born less than 28 weeks of gestation between 2012 and 2017. Outcomes between surgically ligated and pharmacologically treated infants as well as infants born in centers performing ≤10% ligation ("low" group) and >10% ("high" group) were compared using logistic regression and 1:1 propensity score matching. Matching was based on case-mix and preligation confounders: intraventricular hemorrhages grades 3-4, necrotizing enterocolitis, sepsis, and ≥28 days' oxygen supply.

Results Of 1389 infants, 722 (52%) had pharmacologic treatment and 156 (11.2%) received surgical ligation. Compared with infants who received pharmacologic treatment, ligated infants had greater odds for major morbidities (OR 2.09, 95% CI 1.44-3.04) and 2-year neurodevelopmental impairment (OR 1.81, 95% CI 1.15-2.84). Mortality was comparable after restricting the cohort to infants surviving at least until day 10 to avoid survival bias. In the "low" group, 34 (4.9%) of 696 infants were ligated compared with 122 (17.6%) of 693 infants in the "high" group. Infants in the "high" group had greater odds for major morbidities (OR 1.49, 95% CI 1.11-2.0).

Conclusions Our analysis identified a burden on infants receiving surgical ligation vs pharmacologic treatment in a population-based setting where there was no agreed-on common procedure. These results may guide a revision of patent ductus arteriosus treatment practice in Switzerland. *(J Pediatr 2021; ■:1-8)*.

Patent ductus arteriosus (PDA) is a delay in the physiologic closure of the ductus arteriosus that connects the pulmonary artery with the descending aorta. The time it takes to achieve spontaneous closure is inversely proportional to gestational age at birth, with some vessels requiring months to years to close.[1] This delay has been associated with renal dysfunction, intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), chronic lung disease, or retinopathy of prematurity (ROP).[1-3] There is no universally accepted definition or diagnosis; some definitions are based on clinical signs, some require echocardiography, and some require pharmacologic treatment.[4-7] Some clinicians perform diagnosis using routine echocardiography, others require clinical signs, whereas the former will report greater incidences than the latter. Where reported, prevalence is between 20% and 60% among infants born at less than 32 weeks of gestation.[1,2,8] A study of 6 high-income countries (including Switzerland) reported PDA treatment rates ranging from 38% to 52% in infants born less than 28 weeks of gestation and with a birth weight <1500 g.[4] Classical treatment consists of pharmacologic treatment with cyclo-oxygenase inhibitors (usually indomethacin or ibuprofen) or surgical ligation if the medication should fail or be contraindicated. However, this approach has been challenged, and it therefore remains unclear whether and when a pharmacologic or surgical approach is advantageous.[1,9,10]

The uncertainty in clinical diagnosis and management of PDA has led to widespread treatment variation among healthcare providers.[4,7,11,12] The aim of our study was to analyze the variation among Swiss perinatal centers, to assess the

BWZ	Birth weight z score
DOL	Day of life
IVH	Intraventricular hemorrhage
LOS	Late-onset sepsis
NDI	Neurodevelopment impairment
NEC	Necrotizing enterocolitis
O_2	Oxygen
PDA	Patent ductus arteriosus
ROP	Retinopathy of prematurity

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association of surgical ligation with short-term outcome after primary hospitalization and long-term neurodevelopmental outcome at 2 years, and to ascertain whether performing fewer surgical ligations is associated with outcome. Previous attempts report a lower mortality for ligation vs pharmacotherapy without analyzing a potential survival bias.[2,9] Others associate adverse outcome with surgical ligation without analyzing confounding by indication, ie, major morbidities that may serve as indication for surgical ligation and could explain why infants with ligation are associated with worse outcome.[2,9] We attempted to correct both issues by restricting our analysis to infants comparable for ligation without survival bias and by adding preligation confounders to a model matching infants with and without surgical ligation.

Methods

This was a population-based, retrospective cohort study including all live born infants between $22^{0/7}$ and $27^{6/7}$ weeks of gestation in Switzerland from 2012 to 2017 who were admitted to the neonatal ward. We excluded 27 infants born and treated exclusively in 3 stepdown units, 87 infants born with a major congenital malformation (defined as being the primary cause of death or requiring surgery or having a chromosomal anomaly), and 235 infants who died in the delivery room. The Swiss Neonatal Network & Follow-up Group (SwissNeoNet) collects data prospectively and electronically for cohort studies.

Data collection and evaluation for this study were approved by the Swiss Association of Research Ethics Committees (BASEC PB_2016-02299 and 2020-02443). Participating centers were obliged to inform parents about the scientific use of anonymized data.

PDA was defined as symptomatic PDA, requiring pharmacotherapy (indomethacin, ibuprofen, or paracetamol) or surgical ligation. Most PDAs were confirmed by echocardiography by an in-house cardiologist. All but one smaller center diagnosed PDA by performing routine echocardiography. Gestational age was collected as the best-estimate available based on prenatal ultrasound examination during the first trimester of pregnancy. One day of oxygen (O_2) was defined as oxygen support ≥12 hours above room air concentration. Birth weight z scores (BWZ), IVH grades 3-4, NEC as of Bell stage ≥2, late-onset neonatal sepsis (LOS), and ROP stages 3-4 were defined as previously published.[13,14] Major morbidity was a composite outcome of either IVH, NEC, LOS, O_2 requirement ≥28 days, or ROP. Moderate-to-severe neurodevelopmental impairment (NDI) at 2 years of age was a composite outcome including mental, motor, and sensory function as previously described.[13,14]

Patient population coverage was assessed by comparison with the birth registry of the Swiss Federal Statistical Office and yielded 91% of all live births between 22 and 27 weeks of gestation. Data completeness and plausibility were checked on electronic data entry. Missing data were requested until completed. Each center is subject to data audits every 3 years whereby SwissNeoNet verifies a random sample of 10% of the submitted datasets with the original patient file. Accuracy is high (>95% of items). Data on ROP were missing in 1.5% of surviving infants; the rate of follow-up at 2 years of age was 84%. All other data were complete.

We performed propensity score matching to compare infants with surgical ligation (cases) with infants with pharmacotherapy (controls) and to compare infants born in centers with greater than 10% surgical ligation (cases) with those born in centers with lower than 10% (controls). Propensity scores, ie, the probability of being in the case cohort, were estimated from a logistic regression model that included the covariates gestational age, BWZ, sex, being outborn, and having either of the major morbidities IVH, NEC, LOS, or ≥28 days O_2 before surgical ligation (preligation confounders). Each observation from the case cohort was matched to one entry from the control having the closest propensity score.

Preligation confounders were added to the model as these incidents could serve as an indication for ligation. They include all IVH if ligation occurred after day of life (DOL) 3, as the risk of developing IVH is greatest during the first 72 hours of life and we did not have the information on exact onset DOL for IVH.[15] They further include all NEC and LOS if ligation occurred after the onset day of NEC or LOS, and for all occurrences of 28 days O_2 treatment if ligation occurred after DOL 28. Morbidities occurring after DOL 40 in nonligated infants were not included, as >95% of ligations took place beforehand.

Statistical Analyses

We used the χ^2 test with the Yates correction for categorical and the Mann–Whitney *U* test for metric variables. We performed multivariable adjusted logistic regression to compare outcomes between infants with and without surgical ligation and between infants born in centers with lower or higher than 10% surgical ligation. Adjustment was made for gestational age, BWZ, male sex, and outborn births. Other than in the propensity score modeling, preligation confounders were not added to the regression models, as they would introduce bias by unilaterally adjusting for morbidities of infants with surgical ligation if only those incidences count that occur before a ligation, or morbidities of infants without surgical ligation, as they could be interpreted as potential indication for ligation as well. All statistical analyses were performed using R, Version 3.6.1 (R Foundation for Statistical Computing).[16]

Results

A total of 1389 infants were admitted to the 9 Swiss perinatal centers between 2012 and 2017; 722 (52%) received pharmacotherapy and 156 (11.2%) received surgical ligation for a PDA (**Table I**). Of the 156 infants with surgical ligation, 15

Table I. Baseline characteristics and crude outcome, infants <28 weeks of gestation for 2012-2017

Characteristics	All infants	PDA ligation vs no PDA ligation (all infants)			PDA ligation vs no PDA ligation (survivors until day 10)			Treatment in units with low vs high proportion of PDA ligation		
		No PDA ligation	PDA ligation	*P* value	No PDA ligation	PDA ligation	*P* value	High	Low	*P* value
N (2012-2017)	1389	1233 (88.8%)	156 (11.2%)		1069 (87.6%)	151 (12.4%)		693 (49.9%)	696 (50.1%)	
Gestational age, wk (IQR)	26.3 (25.3-27)	26.4 (25.3-27.1)	25.6 (24.6-26.4)	< .001	26.6 (25.6-27.3)	25.6 (24.7-26.4)	< .001	26.4 (25.3-27.1)	26.3 (25.1-27)	.015
BWZ (IQR)	−0.1 (−0.7 to 0.4)	−0.1 (−0.7 to 0.4)	−0.2 (−0.8 to 0.2)	.12	0 (−0.6 to 0.4)	−0.2 (−0.8 to 0.3)	.019	−0.1 (−0.6 to 0.3)	−0.1 (−0.8 to 0.4)	.87
Sex male, No. (%)	723 (52.1 %)	632 (51.3%)	91 (58.3%)	.114	549 (51.4%)	87 (57.6%)	.176	358 (51.7%)	365 (52.4%)	.812
Outborn, No. (%)	66 (4.8%)	60 (4.9%)	6 (3.8%)	.715	48 (4.5%)	4 (2.6%)	.405	37 (5.3%)	29 (4.2%)	.368
PDA, No. (%)	761 (54.8%)	605 (49.1%)	156 (100%)	<.001	534 (50%)	151 (100%)	<.001	368 (53.1%)	393 (56.5%)	.228
Pharmacologically treated PDA, No. (%)	722 (52%)	605 (49.1%)	117 (75%)	0	534 (50%)	117 (77.5%)	0	336 (48.5%)	386 (55.5%)	.011
Surgical PDA ligation, No. (%)	156 (11.2%)	0 (0%)	156 (100%)	<.001	0 (0%)	151 (100%)	<.001	122 (17.6%)	34 (4.9%)	<.001
Day of surgical PDA ligation (IQR)	14 (8-23.5)	N/A	14 (8-23.5)	–	N/A	15 (9.5-24)	–	12 (7-20)	23 (18-30)	<.001
LOS, No. (%)	278 (20%)	229 (18.6%)	49 (31.4%)	<.001	208 (19.5%)	49 (32.5%)	<.001	141 (20.3%)	137 (19.7%)	.809
Severe IVH, No. (%)	196 (14.2%)	170 (13.9%)	26 (16.7%)	.418	100 (9.4%)	24 (15.9%)	.019	87 (12.7%)	109 (15.8%)	.118
NEC stage ≥2, No. (%)	82 (5.9%)	64 (5.2%)	18 (11.5%)	.003	50 (4.7%)	18 (11.9%)	.001	55 (7.9%)	27 (3.9%)	.002
>28 days O_2, No. (%)	837 (60.3%)	705 (57.2%)	132 (84.6%)	<.001	703 (65.8%)	132 (87.4%)	0	412 (59.5%)	425 (61.1%)	.576
Severe ROP, No. (%)	78 (7%)	59 (6.1%)	19 (13.5%)	.002	59 (6.1%)	19 (13.5%)	.002	40 (7.1%)	38 (6.9%)	.978
Child died at any time, No. (%)	257 (18.5%)	242 (19.6%)	15 (9.6%)	.003	78 (7.3%)	10 (6.6%)	.895	123 (17.7%)	134 (19.3%)	.514
Death or major morbidity, No. (%)	641 (46.1%)	542 (44%)	99 (63.5%)	<.001	378 (35.4%)	94 (62.3%)	<.001	339 (48.9%)	302 (43.4%)	.044
Major morbidity, No. (%)	558 (40.2%)	464 (37.6%)	94 (60.3%)	<.001	359 (33.6%)	92 (60.9%)	<.001	299 (43.1%)	259 (37.2%)	.028
Follow-up 2 has taken place, No. (%)	953 (84.2%)	831 (83.9%)	122 (86.5%)	.49	831 (83.9%)	122 (86.5%)	.49	480 (84.2%)	473 (84.2%)	1
Moderate-to-severe NDI at 2 y, No. (% of infants with follow-up)	203 (21.4%)	163 (19.7%)	40 (32.8%)	.001	163 (19.7%)	40 (32.8%)	.001	107 (22.4%)	96 (20.3%)	.50

N/A, not available.

(9.6%) died (Table I). This contrasts with the 242 (19.6%) infants who died among the 1233 infants without ligation. During DOL 1-10, 5 (3.2%) of the infants with ligation died, whereas 164 (13.3%) of the infants without ligation died. A Kaplan–Meier survival plot that simultaneously displays the cumulative proportion of infants with ligation over time (Figure 1) reveals however, that the majority of surgical ligations were performed during a time when fewer infants died. Comparing infants with and without surgical ligation within the entire cohort (Table I) would therefore constitute a survival bias. Instead, we chose DOL 10 as threshold to include as many infants with ligation as possible within a time period in which mortality was lower than is usually observed during the first days after birth in infants born extremely preterm. Table I reveals the cohort restricted to infants who survived at least until DOL 10. All further comparisons between infants with and without surgical ligation are based on this cohort, within which infants with ligation had lower median gestational age (25.6 vs 26.6), lower median BWZ (−0.2 vs −0.1), greater proportions of LOS (32.5% vs 19.5%), IVH (15.9% vs 9.4%), NEC (11.9% vs 4.7%), need of O_2 ≥28 days (87.4% vs 65.8%), ROP (13.5% vs 6.1%), and NDI (32.8% vs 19.7%). However, mortality was similar to that of infants without ligation (6.6% vs 7.3%).

After we adjusted for case-mix in a logistic regression, infants with ligation had a greater odds ratio for death or major morbidity (OR 2.21, 95% CI 1.52-3.2), major morbidity (OR 2.33, 95% CI 1.61-3.36), and NDI (OR 1.86, 95% CI 1.21-2.85) among the survivors until DOL 10 (Figure 2, A, panel I). When we restricted the comparison to the 54.8% infants at risk of adverse outcome due to PDA, ie, infants with either pharmacotherapy or surgical ligation, the odds for adverse outcome of infants with ligation were modestly reduced (Figure 2, A, panel II).

To account for the possibility that infants received surgical ligation because of their worse condition (confounding by indication) vs developing the worse condition after or because of the ligation, we performed propensity score matching: one infant with ligation was matched with one pharmacologically treated infant who had the closest propensity score after including case-mix and preligation confounders. Infants with ligation had greater ORs for death or major morbidity (OR 2.05, 95% CI 1.41-2.98), major morbidity (OR 2.09, 95% CI 1.44-3.04), and NDI at 2 years (OR 1.81, 95% CI 1.15-2.84) (Figure 2, A, panel III).

Using propensity score matching based on case-mix and preligation confounders, we matched the 49 infants with ligation during DOL 1-10 with those 49 pharmacologically treated infants who had the nearest propensity score as a sensitivity analysis. OR for mortality in infants with ligation was 1.05 (95% CI 0.5-2.2).

Four of the Swiss centers performed surgical ligations on >10% of their infants (range 13.9%-22.4%), 5 on <10% (range 0%-9.1%). We split our collective into a group of infants born in centers with a "high" proportion (n = 122/693; 17.6%) vs those born in centers with a "low" proportion

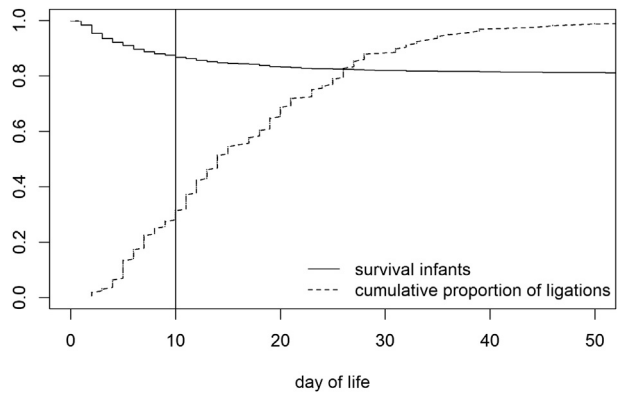

Figure 1. Kaplan–Meier survival plot and cumulative proportion of PDA ligations. Note: none of the infants were censored during the period displayed.

(n = 34/696; 4.9%) of surgical ligation (**Table I**). The 10% threshold was chosen arbitrarily to form 2 groups of similar size. Infants in the "high" group had a slightly greater median gestational age (26.4 vs 26.3), a greater proportion of NEC (7.9% vs 3.9%), and a tendency toward lower proportion of IVH (12.7% vs 15.8%). In the "high" group, surgical ligations were performed generally earlier (median DOL = 12) than in the "low" group (median DOL = 23). **Table II** lists the individual centers ordered by the proportion of infants with ligation. None of the listed center characteristics follow the exact same pattern.

Infants born in centers with high proportion of surgical ligations had greater odds for death or major morbidity (OR 1.45, 95% CI 1.15-1.83) and greater odds for major morbidity (OR 1.42, 95% CI 1.13-1.78). Restricting the cohort to infants at risk of adverse outcome due to PDA, ie, infants who received either pharmacotherapy or surgical ligation, revealed similar results (**Figure 2**, B, panel II).

We repeated the propensity score matching for the comparison between infants born in centers with high vs low proportion of surgical ligation. Infants with PDA from the high and low group were matched for case-mix and preligation confounders. As result, infants in the high group had greater odds for death or major morbidity (OR 1.49, 95% CI 1.11-2) and major morbidity (OR 1.39, 95% CI 1.04-1.87) (**Figure 2**, B, panel III).

Discussion

We present a population-based, geographically defined cohort study, in which infants with surgically ligated PDA were consistently associated with worse short- and long-term outcome compared with infants receiving pharmacologic treatment only, in crude, case-mix adjusted. and propensity score analysis matched for case-mix and preligation confounders. For this analysis, the cohort was restricted to infants who survived at least until DOL 10. DOL 10 was chosen because the majority of surgical ligations took place at the period after DOL 10 when mortality was more stable (**Figure 1**). A comparison of the entire cohort as of DOL 1 would have introduced a selection bias benefitting infants with surgical ligation, as more infants without ligation would have been selected during the period in which mortality is generally greatest among infants born extremely preterm born whereas infants with ligation would have predominantly been selected later. In a second analysis, involving the entire cohort, infants born in centers with greater than 10% surgical ligations had greater odds for adverse short-term outcome than infants born in centers in which fewer than 10% were ligated.

The proportion of infants treated for PDA in Switzerland (54.8%) is somewhat greater than those of 5 other nations recently reported by Isayama et al (range 34%-51%). Their reported proportion of surgical ligation (range 6%-17%) is comparable with ours (11.2%).[4]

Swiss adolescents who were surgically ligated during their primary hospitalization reported lower health-related quality of life than their peers.[17] Other authors report adverse outcome after 2 years associated with surgical ligation, particularly when selective criteria are missing.[18,19] In an extensive review, Weisz and McNamara list biological and clinical evidence for a possible causal effect of surgical ligation on chronic lung disease, ROP, and NDI.[2] In a parallel systematic review, they identify 40 observational studies that associated surgical ligation with lower mortality but increased adverse outcome after primary hospitalization and at 2 years of life. Nearly all of these studies had at least a moderate risk of bias mainly due to failure to adjust for survival bias and important postnatal preligation confounders.[9] Recent studies, however, approach these issues. Mirea et al compared neonatal outcomes according to PDA treatment assignment.[20] After adjustment for confounders, infants with ligation had lower mortality but greater odds of bronchopulmonary dysplasia, NEC, and ROP, compared with pharmacologically treated infants. In a similar attempt to account for survival bias, they restricted the comparison to infants surviving the first 3 days. Had we made the same restriction at 3 instead of 10 days, we would also report lower odds for mortality for infants with rather than without surgical ligation (0.49, 95% CI 0.27-0.88). We, however, argue that in our case the comparison would still contain a selection bias as the bulk of infants with ligation was recruited at a time when survival was stable (**Figure 1**). The propensity score matching performed by Mirea et al also revealed greater adverse outcome for infants with surgical ligation. They, however, did not include preligation confounders into their model.[20] In a recent multicenter study comparing pharmacologically treated vs ligated infants, Weisz and McNamara found no increased morbidities associated with surgical ligation using weighted logistic regression including preligation confounding. To account for survival bias, they restricted their cohorts at DOL 7, 14, 19, and 28. Only at DOL 28 did they no longer see a lower mortality associated with PDA ligations.[5,21] In contrast to our study, cases of PDA were included after fulfilling a measure of severity (defined as ductal diameter

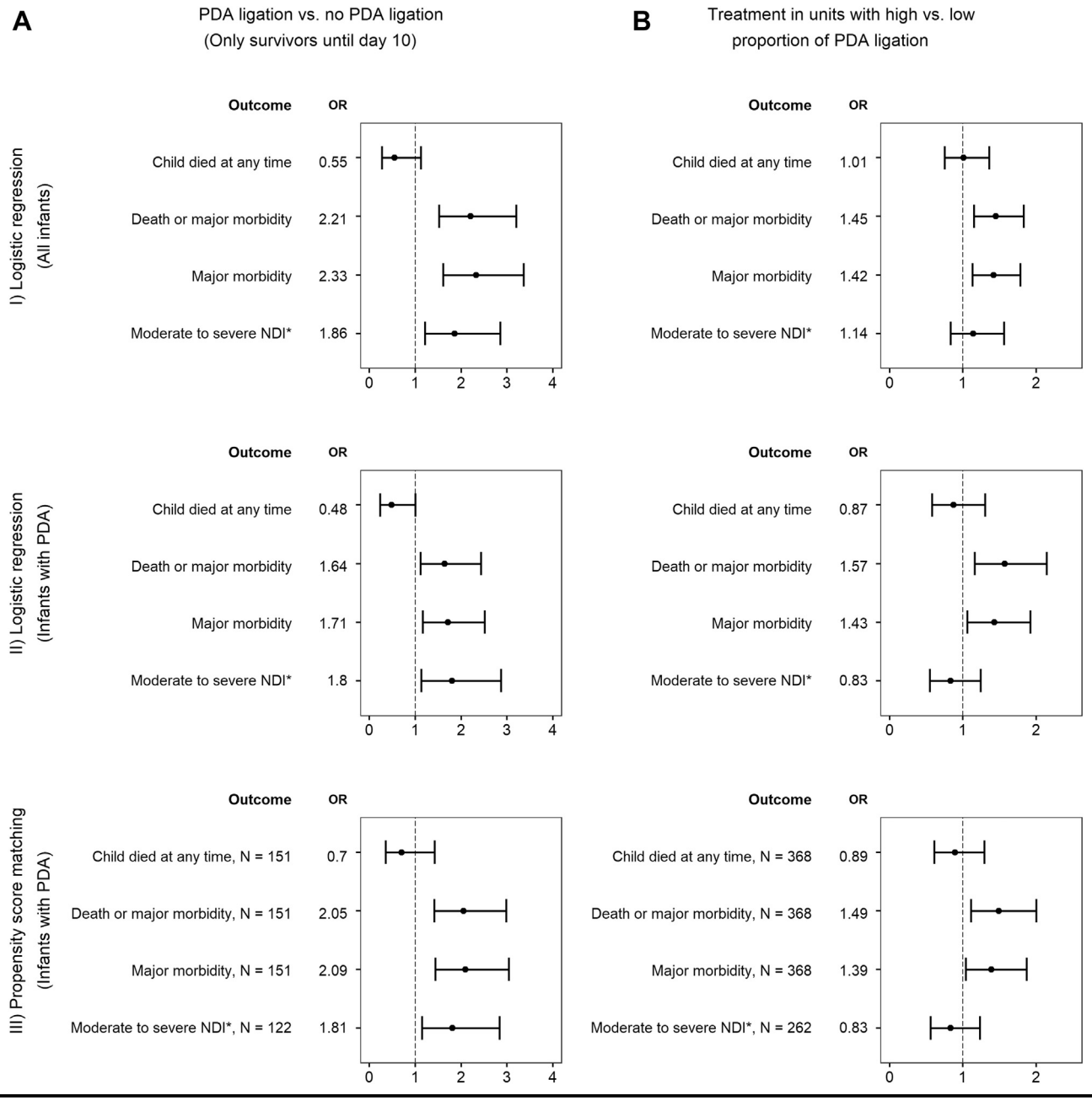

Figure 2. OR for adverse outcome of **A,** infants with PDA ligation vs no PDA ligation and **B,** infants in unit with low vs high proportion of PDA ligation. Major morbidity includes IVH grades 3-4, NEC (Bell stage 2 or greater), late-onset sepsis, O_2 support ≥28 days, and ROP stages 3-4. *Infants assessed at 2-year follow-up. *N*, number of matched cases.

≥1.5 mm on at least 1 echocardiogram) and were compared with surgical ligations that were performed in 3 centers according to an agreed-on protocol after failure of pharmacologic treatment. Their aim was to analyze outcome difference between hemodynamically significant PDA with pharmacotherapy vs surgical ligation, whereas ours was to analyze the variation in outcome between centers in a population-based setting when no universally agreed treatment protocol exists.

We further analyzed this variation by comparing infants treated in centers with high (>10%) and low (<10%) proportion of ligation. It is noteworthy that infants of centers of the high group showed greater odds for adverse outcome even after restricting the analysis to infants with PDA. The individual proportions of major morbidities of infants treated in the 9 perinatal centers reveals that those treated in centers of the high group did not by chance follow the pattern of potentially better vs worse outcome (**Table II**). The individual center's outcome may be influenced by a large selection of factors not included in our analysis, such as antenatal/obstetrical management, approaches to respiratory treatment, feeding practices, etc. However, as our analysis focuses on surgical

Table II. Grouping and characteristics of perinatal centers

	Perinatal center group			Center characteristics		
Centers	Group	Treated PDA	Surgical PDA	Delivery room deaths	Major morbidities	Local pediatric cardiac surgery
Center 1	Low	83 (59.3%)	0 (0%)	8 (5.4%)	42 (28.4%)	No
Center 2	Low	32 (65.3%)	2 (4.1%)	2 (3.9%)	18 (35.3%)	No
Center 3	Low	207 (70.2%)	15 (5.1%)	46 (13.5%)	128 (37.5%)	Yes
Center 4	Low	50 (54.9%)	6 (6.6%)	25 (21.6%)	42 (36.2%)	No
Center 5	Low	14 (11.6%)	11 (9.1%)	32 (20.9%)	29 (19%)	No
Low total		386 (55.5%)	34 (4.9%)	113 (14%)	259 (32%)	
Center 6	High	93 (56.4%)	23 (13.9%)	41 (19.9%)	81 (39.3%)	Yes
Center 7	High	118 (52.2%)	35 (15.5%)	57 (20.1%)	89 (31.4%)	Yes
Center 8	High	43 (32.6%)	26 (19.7%)	13 (9%)	42 (29%)	No
Center 9	High	82 (48.2%)	38 (22.4%)	11 (6.1%)	87 (48.1%)	Yes
High total		336 (48.5%)	122 (17.6%)	122 (15%)	299 (36.7%)	
Total		722 (52%)	156 (11.2%)	235 (14.5%)	558 (34.4%)	

Table is ordered by ascending proportion of surgical PDA.

ligation and we compared infants from both groups after propensity score matching for case-mix and preligation confounding and restricted the cohort to infants receiving treatment for PDA, the greater odds for adverse outcome for infants of the high group may well be associated to their center's approach to surgical ligation.[2,22-24] The centers of the low group also did not have more delivery room deaths. Thus, a survival bias by which infants at risk for PDA died before being diagnosed can be ruled out (**Table II**), nor is there an unambiguous geographic or organizational pattern (type of center, size, or staffing) by which the centers are grouped other than the greater representation of local pediatric cardiac surgery departments on the side of the high group. All centers fulfill Swiss standard requirements for neonatal intensive care.[25] It is therefore not conceivable why infants born in one-half of the Swiss centers should require 3 times as many ligations than the other one-half. The observed variation between these 2 center groups may therefore fulfill Wennberg's definition of being preference sensitive, where treatment rates can vary extensively because of differences in professional opinion, or even supply sensitive, ie, where care comprises clinical activities for which the frequency of use relates to the capacity of the local healthcare system rather than evidence based need.[26] As infants of our cohort receiving surgical ligation vs pharmacotherapy have worse outcome, this variation is unwarranted and may have a harmful effect.

Other studies have reported similar variation among perinatal centers.[7,11,12] Despite large treatment differences, a study from the Netherlands showed no difference in short-term morbidity; however, perinatal center was a significant predictor in a multivariable logistic regression.[7] A study from the United Kingdom reports significant variations in the number of babies receiving pharmacotherapy in different centers by neonatologists claiming to follow the same treatment strategy.[12] In the US, a survey reported a significantly increased likelihood that a neonatologist would ligate a PDA in infants who did not require mechanical ventilation if the neonatologist believed that feedings had to be stopped because of the PDA.[11] In an analysis of treatment and outcome variation among 6 countries including 139 centers, both low and high PDA treatment rates (combining pharmacotherapy and ligation) were associated with death or severe neurologic injury, whereas a moderate approach was associated with optimal outcome.[4]

In our study, we also observed that centers of the low group performed surgical ligations later than those of the high group. According to Benitz, delaying ligation may have advantages, as it avoids surgery in many infants in whom the ductus closes without treatment and reduces the risk of postoperative hemodynamic compromise in those who require surgery.[22] Other studies reported no disadvantage for a late vs early approach to surgery for short- or long-term outcome.[18,27]

Our study has strengths and limitations. We evaluated prospectively collected population-based data appraised for accuracy and with a representative follow-up rate at 2 years of age of 84%. We included case-mix and preligation confounding and examined 2 forms of survival bias. Limitations concern the heterogeneity between centers in the diagnosis and pharmacotherapy of infants with PDA. This may explain some of the variation in the proportion of pharmacotherapy per center (**Table II**), which, however, did not follow that of surgical ligation. There is limited precision in determining preligation confounding for IVH as we did not record an onset DOL for IVH but instead assumed onset within the first 72 hours for all IVH. This, however, favors the ligation side of propensity score modeling, as each IVH counted as potential indication for any ligation after DOL 3. Although the treating center has been shown to be a determinant of ligation frequency and outcome, we did not add it as co-factor to either of the analyses, as this would have adjusted the analysis for their effect on outcome. One of our aims, however, was to reveal the effect that centers can have on outcome. For the sake of completeness, we display the outcome difference for infants with ligation additionally adjusted for treating center in **Figure 3**, A (available at www.jpeds.com). Restricting the comparison between pharmacologically and surgically treated infants with PDA to infants surviving at least until DOL 10 removes some infants with PDA who died during this period who may

potentially have benefited from surgery. However, a sensitivity analysis comparing the outcome of infants who were ligated during the first 10 DOL to propensity score matched pharmacologically treated infants reveals no lower odds for mortality during this period. Nevertheless, our result regarding the lack of association between surgical ligation and mortality has to be treated with caution. For the sake of completeness, we added an analysis that compares infants with and without surgical ligation using the cohort of all infants as of DOL 1 (**Figure 3**, B; available at www.jpeds.com).

In conclusion, although the benefit of surgical ligations should be considered for infants with severe forms of PDA, our analysis places a clear burden on surgical ligation vs pharmacotherapy in a population-based setting without evidence-based guidelines. Infants born in centers with more than 10% (median 17.6%) vs less than 10% surgical ligation (median 4.9%), with ligation rates not following an unambiguous geographical or organizational pattern, had greater odds for adverse outcome. The combination of greater odds for adverse outcome for children receiving surgical ligation on the one hand and children born in centers performing more surgical ligations on the other reveals an unwarranted preference or supply-sensitive variation that could be addressed to improve overall outcome. ■

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Data Statement

Additional data are available by emailing mark.adams@usz.ch.

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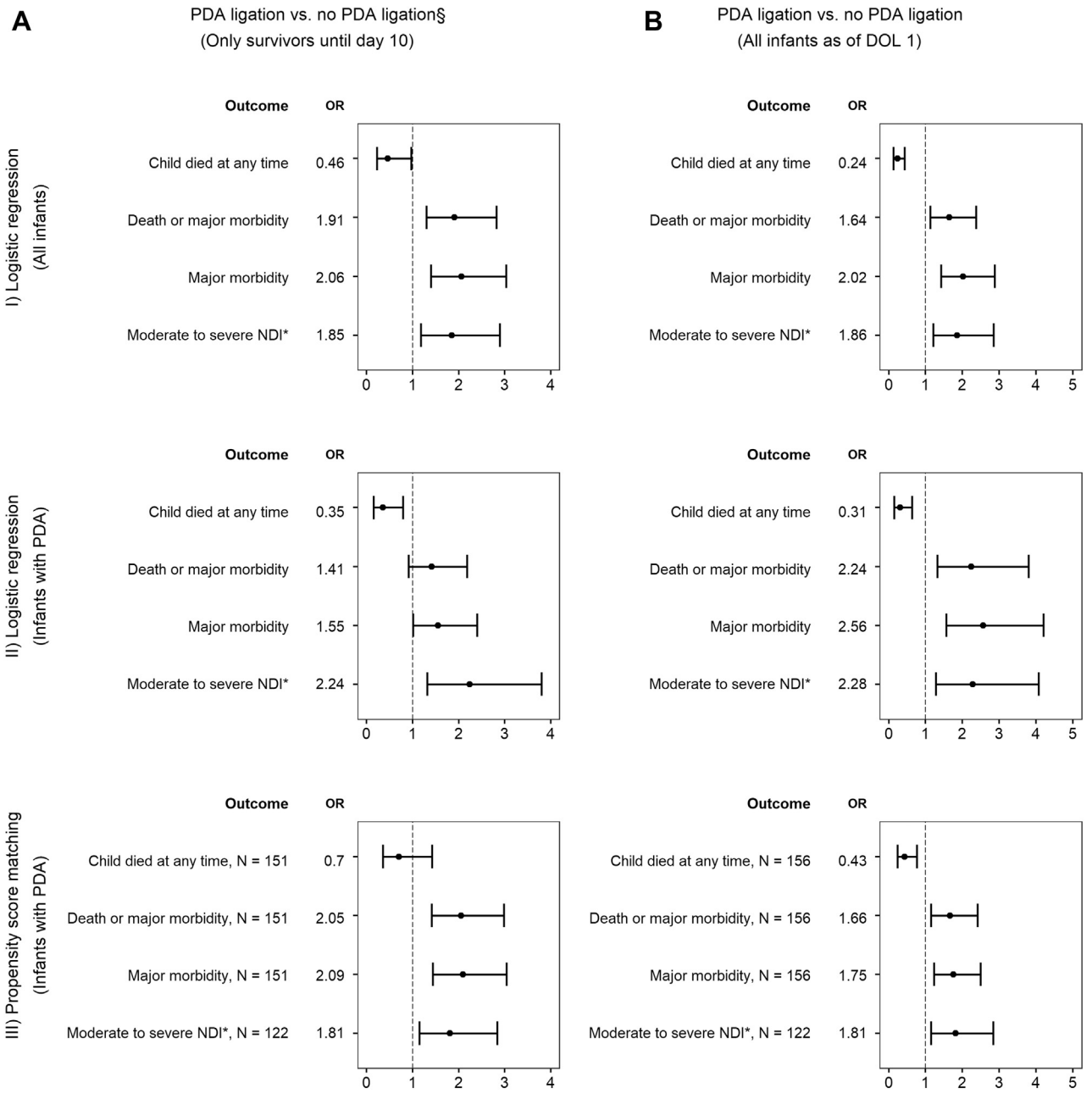

Figure 3. OR for adverse outcome of **A,** infants with PDA ligation vs no PDA ligation as of DOL 10 and **B,** infants with PDA ligation vs no PDA ligation as of DOL 1. Major morbidity includes IVH grades 3-4, NEC (Bell stage 2 or greater), LOS, O_2 support ≥28 days, and ROP stages 3-4. *Infants assessed at 2-year follow-up. §Including treating center as co-factor.