Treatment of patent ductus arteriosus and short-term outcomes among extremely preterm infants: a multicentre cohort study

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Summary

Background The optimal treatment strategy for patent ductus arteriosus (PDA) in extremely preterm infants is currently highly controversial. This study aimed to evaluate the association between PDA treatment and short-term outcomes among extremely preterm infants.

Methods This cohort study included all extremely preterm infants (≤27 and 6/7 weeks) who were admitted to hospitals participating in the Chinese Neonatal Network from January 2019 to December 2021, and were diagnosed to have PDA by echocardiogram. PDA treatment was defined as medical treatment and/or surgical ligation of PDA during hospitalization. Short-term outcomes included death, bronchopulmonary dysplasia (BPD), death/BPD, retinopathy of prematurity, necrotizing enterocolitis, and severe brain injury. Multivariate logistic regression was used to evaluate the association between PDA treatment and outcomes. Subgroup analysis were performed among infants with different respiratory support on 3 and 7 days of life.

Findings A total of 2494 extremely preterm infants with the diagnosis of PDA were enrolled, of which 1299 (52.1%) received PDA treatment. PDA treatment was significantly associated with lower risk of death (adjusted odds ratio, 0.48; 95% confidence interval, 0.38–0.60). The decreased risk of death was accompanied by increased risk of BPD and death/BPD. In subgroup analysis according to respiratory support, PDA treatment was associated with lower risk of death among infants who required invasive ventilation. However, the beneficial effect on death was not significant among infants who did not require invasive ventilation.

Interpretation PDA treatment was associated with reduced mortality in extremely preterm infants, but this beneficial effect was mainly present among infants who required invasive ventilation.

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Keywords: Patent ductus arteriosus; Extremely preterm infants; Preterm infants; Treatment

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Research in context

Evidence before this study

Patent ductus arteriosus (PDA) is a common condition among extremely preterm infants (born at less than 28 weeks of gestation). The optimal treatment strategy for PDA is currently highly controversial. We searched PubMed for English-language research articles published before 1 March 2023 using "patent ductus arteriosus" and "preterm infant" as search terms. Previous studies in recent years have shown that PDA treatment did not improve outcomes, prompting calls not to treat PDA in preterm infants actively. Nevertheless, these studies included relatively small proportions and absolute numbers of extremely preterm infants who are the most vulnerable population to the harm of PDA, homogenised infants with different severity of disease, focused mainly on composite outcomes, and authorised rescue therapy in the non-treatment group. All of these may bias the effect of PDA treatment.

Added value of this study

This study enrolled currently the largest multicentre cohort of extremely preterm infants with the diagnosis of PDA to assess an important clinical question, whether PDA treatment is associated with improved outcomes in these most vulnerable infants. We found that PDA treatment was associated with reduced mortality in extremely preterm infants, but this beneficial effect was mainly present among infants who required invasive ventilation.

Implications of all the available evidence

We identified a subgroup of extremely preterm infants who would benefit from PDA treatment. This finding partially explains the conflicting results of previous studies. More importantly, this finding suggests that PDA treatment in extremely preterm infants may be necessary, while highlighting the necessity of judicious treatment indications. Further studies with more precise treatment criteria are needed to identify the subgroup of extremely preterm infants who could benefit most from PDA treatment.

Introduction

Patent ductus arteriosus (PDA) is a common condition among extremely preterm infants (born at less than 28 weeks of gestation). Left-to-right shunting of PDA in premature infants is thought to lead to high pulmonary blood flow and systemic hypoperfusion, and is associated with mortality and morbidities such as necrotizing enterocolitis (NEC), intraventricular haemorrhage (IVH), bronchopulmonary dysplasia (BPD), and retinopathy of prematurity (ROP).[1,2] The optimal treatment strategy for PDA is currently highly controversial.[1,2] Clinically, medical treatment has been widely used to close the ductus arteriosus, with data from several large national and international cohort studies showing that a large proportion (21–51%) of very low birth weight infants were medically treated for PDA.[3–8] However, several randomised clinical trials[9–12] and observational cohort studies[13–16] in recent years have shown that PDA treatment did not improve outcomes, prompting calls not to treat PDA in preterm infants actively. Nevertheless, these studies included relatively small proportions and absolute numbers of extremely preterm infants[10,13–16] who are the most vulnerable population to the harm of PDA, homogenised infants with different severity of disease,[12–16] focused mainly on composite outcomes,[10,12,13,15] and authorised rescue therapy in the non-treatment group.[9,11] All of these may bias the effect of PDA treatment.

In this study, our objective was to examine the association between PDA treatment and short-term outcomes among extremely preterm infants using a large cohort from the Chinese Neonatal Network (CHNN). Moreover, we performed subgroup analyses based on sex, gestational age (GA) and disease severity, and the outcomes were not limited to the composite measure. This approach aimed to determine whether there was a subgroup of infants who might benefit the most from PDA treatment.

Method

Data source

This cohort study used data prospectively collected in the CHNN database. CHNN has established and maintained a standardised national clinical database of very preterm or very low birth weight infants (GA< 32 weeks or birth weight <1500 g) in tertiary neonatal intensive care units (NICUs) to monitor changes in outcomes and care practices and to explore potential strategies for improving neonatal care.[17] The CHNN database was launched on January 1, 2019 with prospective data collection. In 2019, CHNN had a total of 57 NICUs that collected whole-year data of all admitted very preterm or very low birth weight infants. This number increased to 70 NICUs in 2020, and further to 79 NICUs in 2021. All participating NICUs are tertiary referral facilities and were selected to represent neonatal care in different regions of the country.

Data were collected by trained abstractors at each site, and were entered directly from patient charts into a customised database with built-in error checking using a standard protocols and definitions manual. Data were transmitted electronically to the CHNN coordinating centre at Children's Hospital of Fudan University with patient identity kept confidential. The coordinating

centre checked the quality and integrity of data and conducted audits to ensure the quality of data.[18]

Ethics

This study was approved by the ethics review board of Children's Hospital of Fudan University (2018–296) and endorsed by all participating hospitals. Due to the use of de-identified patient data, all sites agreed to waive consent for data collection.

Patients

All extremely preterm infants (GA ≤27 and 6/7 weeks) admitted to CHNN-participating NICUs between January 2019 and December 2021 were assessed for eligibility for this study. Infants with a diagnosis of PDA by echocardiogram were enrolled. Infants were excluded if they were older than 3 days of birth on admission (data on whether PDA treatment was received prior to admission were not available), died or discharged within 3 days after birth (who may not have opportunity for PDA treatment, and including them may lead to overestimation of PDA treatment effects), were transferred to other hospitals, had major congenital anomalies, and had missing PDA diagnostic data. Infants were followed until death or discharge from the NICUs.

Exposure and outcomes

The exposure was PDA treatment, defined as medical treatment and/or surgical ligation of PDA during NICU hospitalization. There is currently no universal guideline for the management of PDA among preterm infants in China, thus allowing for the evaluation of varying practices with differing PDA management strategies. The treatment of PDA followed institutional guidelines and was determined by the attending neonatologists at each centre. PDA was diagnosed based on echocardiography in all CHNN sites, with the general diagnostic criteria being a transductal diameter greater than 1.5 mm and the presence of a predominant left-to-right shunt. Oral ibuprofen and acetaminophen were used for medical treatment for PDA, and indomethacin was not available in China. Prophylactic medical treatment of PDA within 24 h after birth was rarely used. Surgical ligation was performed in infants with PDA unresponsive to, or with contraindications to, medical therapy as per institutional protocols.

Outcomes included death before discharge, BPD, death and/or BPD (death/BPD), NEC ≥ stage II, NEC with surgery, ROP ≥ stage 3, IVH ≥ grade 3, and periventricular leukomalacia.

Definition

BPD was defined as requiring oxygen therapy, positive pressure ventilation, or mechanical ventilation at GA 36 weeks. NEC was defined and staged according to Bell staging.[19] ROP was defined and staged according to ROP international classification.[20] IVH was defined and graded according to Papile criteria.[21] Periventricular leukomalacia was defined as the presence of periventricular cysts on cranial ultrasound or cranial magnetic resonance imaging scans.

Small for gestational age was defined birth weight less than the 10th percentile for the GA according to the Chinese neonatal birth weight values.[22] Antenatal steroids was defined as a partial or complete course of antenatal steroids before birth. Chorioamnionitis was diagnosed clinically or histopathologically. The Transport Risk Index of Physiologic Stability (TRIPS) score was used as the disease severity score on NICU admission.[23,24] TRIPS score was calculated from temperature, respiratory status, systolic blood pressure, and response to noxious stimuli at admission, and was shown to be correlation with NICU mortality.[23,24] Early-onset sepsis was defined as culture-proven sepsis within the first 72 h of life.

Statistics

Data were presented as frequency and percentage, mean with standard deviation (SD), or median with interquartile range (IQR) wherever appropriate. Differences in baseline characteristics between treatment and non-treatment groups were evaluated using χ^2 test for categorical variables and Student t test or Mann–Whitney U test for continuous variables.

Univariate and multivariate logistic regressions were used to calculate the odds ratio of outcomes for PDA treatment vs non-treatment groups. Two multivariate models were generated. In model 1, we adjusted confounders including sex, GA, small for gestational age, cesarean birth, multiple gestation, premature rupture of membranes >24 h, Apgar score at 5 min, use of antenatal steroids, maternal hypertension, chorioamnionitis, TRIPS score, use of caffeine, early illness severity (need for invasive ventilation on day 3, number of surfactant administrations within 3 days after birth, need for inotropes within 3 days after birth, need for transfusion within 3 days after birth), and early-onset sepsis. These confounding variables, summarised from previous literature and based on clinical experience, were pre-determined prior to this study and identified as confounders by a directed acyclic graph (Supplementary Fig. S1). In model 2, we further adjusted for the centre cluster effect using the generalised estimating equation in addition to the confounders in model 1.

We then performed GA subgroup analysis (GA ≤26 and GA >26 weeks) and sex subgroup analysis (male and female) to test whether GA and sex modified the effect of PDA treatment on the outcomes. In addition, the effect of PDA treatment may vary among subgroups of infants with different disease severity. The level of respiratory support may represent the disease severity to

some extent. Therefore, we also conducted subgroup analysis according to the respiratory support (invasive ventilation or no invasive ventilation) to observe whether the effect of PDA treatment varied with disease severity. To ensure the accuracy and reliability of our findings, we selected two time points of respiratory support for subgroup analysis, namely 3 and 7 days after birth. To avoid potential interference from prior treatment, we excluded infants who had received PDA treatment before these two time points (i.e., in subgroup analysis on 3 days after birth, we excluded infants who had received treatment within 3 days of life; in subgroup analysis on 7 days after birth, we excluded infants who had received treatment within 7 days of life). The interaction of respiratory support (on day 3 and day 7) and PDA treatment on outcomes was also evaluated in the multivariable logistic regression models.

To assess the robustness of our results, we performed some sensitivity analyses. First, we used propensity score matching to balance the baseline characteristics of treated and untreated infants to see if the results were robust in the propensity score matched sample. Second, the exclusion of infants admitted after 3 days of age was due to the unavailability of data on PDA treatment prior to admission. However, considering the representativeness of these infants, they were subsequently re-included for sensitivity analysis. Regardless of whether or not they had received PDA treatment prior to admission, we only examined whether or not they had received PDA treatment after admission. Third, we conducted an analysis excluding centres with a small number of cases (<20 extremely preterm infants with PDA). Fourth, infants with PDA ligation may have higher illness severity, resulting in bias in the treatment group. Therefore, we re-ran the analysis in the cohort excluding infants with surgical ligation. Finally, there were 522 (20.9%) missing data for chorioamnionitis, while the proportion of missing data for other variables was less than 10%. Given that the missing data of chorioamnionitis were highly likely to be "non-events", we imputed the missing data of chorioamnionitis as "none" in the multivariable analysis to reflect the actual situation, while the remaining variables were not imputed. To validate the robustness of the regression adjustment results, we also conducted sensitivity analyses in the sample without imputation of missing data for chorioamnionitis.

Statistical analysis was performed using SAS version 9.4. All statistical tests were 2-sided tests, and $P < 0.05$ was considered statistically significant.

Role of the funding source

The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Results

During the study period, a total of 5179 extremely preterm infants with GA ≤27 and 6/7 weeks were admitted to CHNN-participating NICUs. A total of 1534 infants met the exclusion criteria (Fig. 1). Of the remaining 3645 extremely preterm infants, 2494 (68.4%) infants were diagnosed with PDA by echocardiography and were enrolled in our analysis. Overall, 52.1% (1299/2494) infants received PDA treatment, and 47.9% (1195/2494) infants did not receive treatment. Among 1299 infants with PDA treatment, 1213 (93.4%) received medical treatment only, 14 (1.1%) received surgical ligation after medical treatment, and 72 (5.5%) received surgical ligation only. The rate of surgical ligation in infants receiving medical treatment was 1.1% (14/1227), significantly lower than the rate of 5.7% (72/1267) in infants not receiving medical treatment ($\chi^2 = 38.619$; $P < 0.001$). The median postnatal age at first medical treatment and surgical ligation was 7 days (IQR: 4–11) and 33 days (IQR: 27–50), respectively (Distributions of the postnatal age at the first medical treatment and surgical treatment were in Supplementary Fig. S2 and S3). PDA treatment rates (excluding hospitals with less than 20 PDA cases) varied among different NICUs (median: 50%; IQR: 38.0%–65.9%; range: 10.5%–91.0%).

Baseline characteristics

Baseline characteristics of infants in the treatment group and non-treatment group are shown in Table 1. The infants in the treatment group had lower GA, lower birth weight and higher TRIPS score on admission than those in the non-treatment group. Compared with the non-treatment group, the treatment group had higher proportions of invasive ventilation on 3 days and 7 days after birth, surfactant use, and caffeine use.

Association of PDA treatment and neonatal outcomes

In univariate analysis, compared to the non-treatment group, the treatment group had significantly lower mortality (20.6% vs 33.1%), but higher incidence of BPD (57.6% vs 41.1%), death/BPD (64.9% vs 59.1%), and ROP ≥3 (13.4% vs 9.2%). After adjusting for patient confounders, PDA treatment remained independently associated with lower risk of death (adjusted odds ratio [aOR], 0.48; 95% confidence interval [CI], 0.38–0.60; $P < 0.001$), but higher risks of BPD (aOR, 1.77; 95% CI, 1.41–2.22; $P < 0.001$), and death/BPD (aOR, 1.23; 95% CI, 1.01–1.50; $P = 0.042$) (Table 2). Further adjustment of centre cluster effect showed similar results (Table 2).

Subgroup analyses

In both the sex subgroup analysis (male and female) and the GA subgroup analysis (GA ≤26 and GA >26 weeks), PDA treatment was significantly associated with a lower risk of mortality in both male infants (aOR, 0.53; 95%

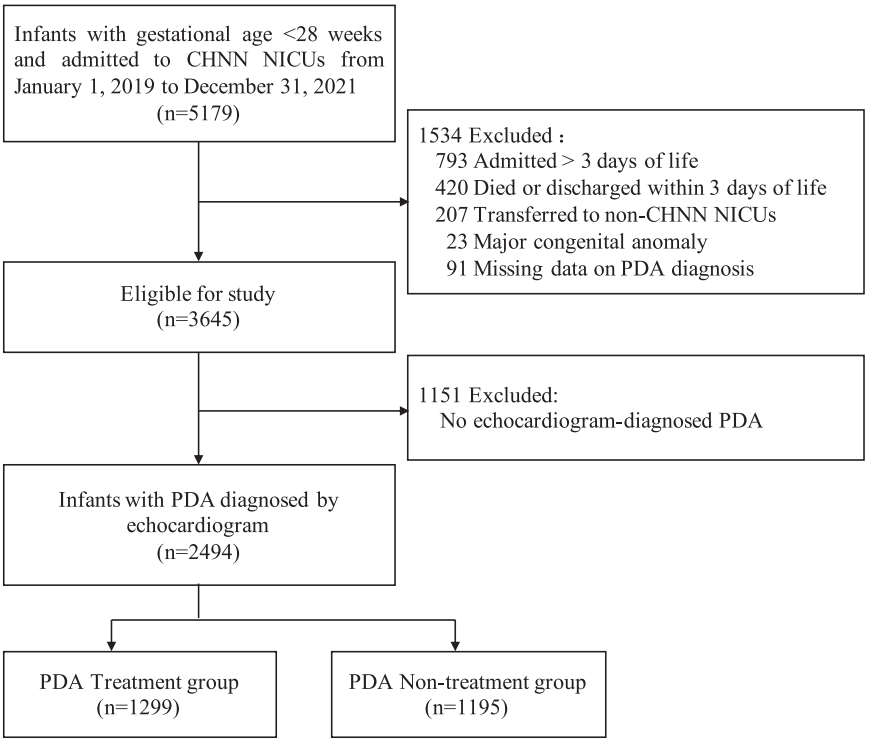

***Fig. 1:* Study population**. Abbreviations: CHNN, Chinese Neonatal Network; NICUs, neonatal intensive care units; PDA, patent ductus arteriosus.

CI, 0.39–0.74; $P < 0.001$) and female infants (aOR, 0.41; 95% CI, 0.28–0.58; $P < 0.001$), as well as infants ≤26 weeks (aOR, 0.48; 95% CI, 0.35–0.66; $P < 0.001$) and infants >26 weeks (aOR, 0.46; 95% CI, 0.32–0.66; $P < 0.001$) (Fig. 2).

In subgroup analysis according to respiratory support on 3 days after birth, PDA treatment was independently associated with a lower risk of death among infants who were on invasive ventilation 3 days after birth (aOR, 0.37; 95% CI, 0.28–0.50; $P < 0.001$). However, the beneficial effect on death was not significant among infants who did not require invasive ventilation on 3 days after birth (aOR, 0.73; 95% CI, 0.47–1.16; $P = 0.183$) (Fig. 2). An interaction was detected between respiratory support on day 3 and PDA treatment in multivariable logistic regression analysis examining the outcome of death (P for interaction = 0.043).

In subgroup analysis based on respiratory support on 7 days after birth, consistent with the result of subgroup on 3 days after birth, a beneficial effect on death was observed among infants who required invasive ventilation (aOR, 0.39; 95% CI, 0.25–0.60; $P < 0.001$). The beneficial effect on death was even less significant among infants who did not require invasive ventilation (aOR, 0.84; 95% CI, 0.50–1.40; $P = 0.497$) (Fig. 2). An interaction was also detected between respiratory support on day 7 and PDA treatment (P for interaction = 0.036).

Sensitivity analyses

In all sensitivity analyses, including propensity score matching, re-including infants admitted after 3 days of age, excluding small centres, excluding infants with surgical ligation, and without imputation of missing data for chorioamnionitis, the association between PDA treatment and lower risk of mortality remained similar to the primary analysis (Supplementary Fig. S4, Supplementary Tables S1–S6).

Discussion

In this multicentre cohort study of 2494 extremely preterm infants with PDA diagnosis, PDA treatment was associated with a significantly decreased risk of death. This beneficial effect of PDA treatment on death was mainly present among extremely preterm infants who required invasive ventilation.

Although the infants in the PDA treatment group were less mature and had higher early disease severity than infants who were in the non-treatment group, we found a significantly decreased risk of death for infants receiving PDA treatment. This result remained significant following sensitivity analyses and subgroup

Variables	Treatment (n = 1299)	Non-treatment (n = 1195)	*P* value
Prenatal or neonatal characteristics			
Sex			0.089
Male, n (%)	716 (55.1%)	699 (58.5%)	
Female, n (%)	583 (44.9%)	496 (41.5%)	
Gestational age, weeks, median (IQR)	26.9 (25.9–27.4)	27.0 (26.0–27.4)	0.003
≤24, n (%)	121 (9.3%)	92 (7.7%)	
25, n (%)	220 (16.9%)	156 (13.1%)	
26, n (%)	347 (26.7%)	329 (27.5%)	
27, n (%)	611 (47.0%)	618 (51.7%)	
Birth weight, g, mean (SD)	930.8 (179.6)	953.8 (182.9)	0.002
Admission age, hours, median (IQR)	0.6 (0.4–1.8)	0.6 (0.3–2.1)	0.121
Small for gestational age, n (%)	29 (2.2%)	25 (2.1%)	0.810
Multiple births, n/N (%)	502/1299 (38.6%)	476/1194 (39.9%)	0.533
Cesarean delivery, n/N (%)	881/1299 (67.8%)	820/1192 (68.8%)	0.603
Apgar at 5 min ≤ 3, n/N (%)	28/1214 (2.3%)	40/1101 (3.6%)	0.059
TRIPS score, median (IQR)[a]	21 (13–28)	19 (8–28)	<0.001
PROM >24 h, n/N (%)	235/1229 (19.1%)	244/1104 (22.1%)	0.075
Antenatal steroids, n/N (%)	951/1208 (78.7%)	822/1101 (74.7%)	0.021
Maternal hypertension, n/N (%)	118/1287 (9.2%)	119/1181 (10.1%)	0.445
Chorioamnionitis, n/N (%)	241/1029 (23.4%)	252/943 (26.7%)	0.091
Clinical characteristics			
Caffeine, n (%)	1245 (95.8%)	1108 (92.7%)	<0.001
On invasive ventilation on day 3, n (%)	750 (57.7%)	628 (52.6%)	0.009
On invasive ventilation on day 7, n (%)	533 (41.0%)	333 (27.9%)	<0.001
Number of PS used within 3 days after birth			<0.001
0, n (%)	206 (15.9%)	288 (24.1%)	
1, n (%)	941 (72.4%)	770 (64.4%)	
≥2, n (%)	152 (11.7%)	137 (11.5%)	
Inotropes used within 3 days after birth, n (%)	392 (30.2%)	377 (31.5%)	0.459
Transfusion within 3 days after birth, n (%)	324 (24.9%)	336 (28.1%)	0.073
Early-onset sepsis, n (%)	36 (2.8%)	25 (2.1%)	0.273

Abbreviations: PDA, patent ductus arteriosus; IQR, interquartile range; SD, standard deviation; TRIPS, Transport Risk Index of Physiologic Stability; PROM, premature rupture of membranes; PS, pulmonary surfactant. [a]TRIPS scores range from 0 to 54. Higher values represent greater illness severity.

Table 1: **Clinical characteristics of PDA treatment and non-treatment groups.**

analyses based on sex and GA. This finding is consistent with data from the Korean national cohort,[6] the EPIPAGE 2 national population-based cohort from France,[4] and the comparative study between Japan and Canada.[3] Pathophysiologically, the consequences of left-to-right shunting through the ductus arteriosus include pulmonary edema, congestive heart failure and reduced systemic blood flow leading to peripheral organ ischemia, which may compromise the survival for extremely preterm infants, and previous studies have shown that persistent PDA was associated with increased mortality in premature infants.[25,26] The accumulated evidence suggests that treatment of PDA in extremely preterm infants may be justified.

However, several prior meta-analyses,[27,28] randomised clinical trials[9–11] and observational cohort studies[13–16] did not show improved outcomes with PDA treatment. There might be several reasons for the conflicting results. First, most studies[10,13–16,27,28] enrolled a large proportion of more mature preterm infants (28–32 weeks), and these infants were more likely to have spontaneous ductal closure and experience less haemodynamic effects from PDA.[29] Pooling data across gestational ages may mask the potential effect of PDA treatment on outcomes for the most immature population. The study of Altit et al. also showed that a non-treatment policy was not associated with increased adverse outcomes among infants between 26 and 29 weeks of GA, but adversely affected infants <26 weeks.[30] Second, some studies used a composite outcome (e.g., death/BPD) as the primary outcome,[13,15] avoiding the effect of survival bias on the composite outcome but ignoring that a decrease in mortality leads to an increase in BPD, making the composite outcome of death/BPD potentially negative. As shown in our study, the decrease in mortality in the treatment group

Outcomes	Treatment (n = 1299), n (%)	Non-treatment (n = 1195), n (%)	Univariate analysis		Model 1[a]		Model 2[b]	
			Crude OR (95% CI)	*P* value	aOR (95% CI)	*P* value	aOR (95% CI)	*P* value
Death	268 (20.6%)	395 (33.1%)	0.53 (0.44–0.63)	<0.001	0.48 (0.38–0.60)	<0.001	0.46 (0.35–0.60)	<0.001
BPD[c]	593/1029 (57.6%)	319/776 (41.1%)	1.95 (1.61–2.35)	<0.001	1.77 (1.41–2.22)	<0.001	1.56 (1.28–1.91)	0.002
Death/BPD	843 (64.9%)	706 (59.1%)	1.28 (1.09–1.51)	0.003	1.23 (1.01–1.50)	0.042	1.14 (0.93–1.40)	0.214
NEC ≥ stage II	87 (6.7%)	63 (5.3%)	1.29 (0.92–1.80)	0.136	1.24 (0.85–1.80)	0.262	1.27 (0.89–1.80)	0.183
NEC with surgery	45 (3.5%)	28 (2.3%)	1.50 (0.93–2.41)	0.099	1.36 (0.79–2.33)	0.265	1.45 (0.89–2.37)	0.133
ROP ≥ stage 3[d]	143/1067 (13.4%)	74/803 (9.2%)	1.52 (1.13–2.05)	0.005	1.41 (0.98–2.02)	0.064	1.38 (0.99–1.91)	0.054
IVH ≥ grade 3[e]	201/1246 (16.1%)	189/1114 (17.0%)	0.94 (0.78–1.17)	0.586	0.94 (0.72–1.24)	0.674	0.92 (0.67–1.26)	0.604
PVL[e]	100/1236 (8.1%)	88/1100 (8.0%)	1.01 (0.75–1.37)	0.936	1.12 (0.78–1.61)	0.527	1.13 (0.76–1.67)	0.554

Abbreviations: PDA, patent ductus arteriosus; OR, odds ratio; CI, confidence interval; aOR, adjusted odds ratio; BPD, bronchopulmonary dysplasia; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity; IVH, intraventricular haemorrhage; PVL, periventricular leukomalacia. [a]Model 1 adjusted for sex, gestational age, small for gestational age, cesarean birth, multiple birth, premature rupture of membranes >24 h, Apgar score at 5 min, use of antenatal steroids, maternal hypertension, chorioamnionitis, Transport Risk Index of Physiologic Stability score, use of caffeine, invasive ventilation on day 3, number of pulmonary surfactant used within 3 days after birth, inotropes within 3 days after birth, transfusion within 3 days after birth, and early-onset sepsis. [b]Model 2 adjusted for covariates in model 1 plus central effect using generalised estimating equation. [c]Among infants alive at 36 weeks of postmenstrual age. [d]Among infants with ROP screening. [e]Among infants with neuroimaging results.

Table 2: **Neonatal outcomes in PDA treatment and non-treatment groups.**

was accompanied by an increase in BPD, resulting in a slight increase in the composite outcome of death/BPD. A study by Slaughter et al.,[15] using an instrumental variable analysis that incorporated clinician preference-based practice variation, reported no association between PDA treatment and the composite outcome of death/BPD. However, in their study, PDA treatment was significantly associated with a reduction in mortality (aOR, 0.57; 95% CI, 0.49–0.67). We considered that death is a more severe adverse outcome compared to the composite outcome of death/BPD. Third, the high rate of rescue treatment in the non-treatment group may be another reason for the negative results.[9,11] An unblinded randomised controlled trial (PDA-TOLERATE) showed no difference in outcomes between the treatment and non-treatment arms.[9] However, 48% of the infants in the non-treatment group eventually received rescue treatment. A post hoc analysis study of PDA-TOLERATE trial showed that 18% of potentially eligible infants were not enrolled and received PDA treatment outside of the PDA-TOLERATE trial due to "lack-of-physician-equipoise",[31] and these infants had a significantly lower mortality rate compared to those enrolled in the PDA-

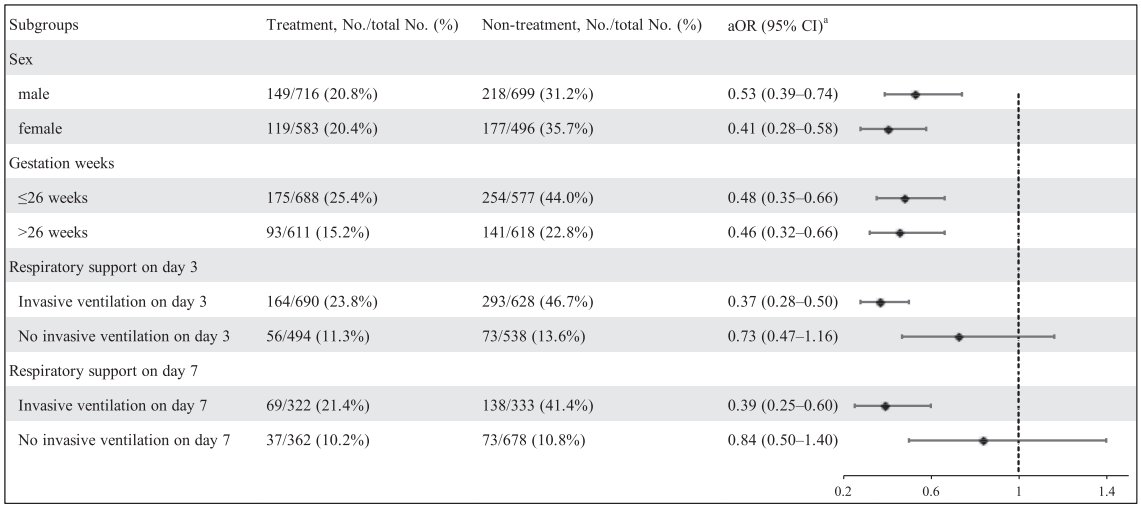

Fig. 2: **Mortality in PDA treatment and non-treatment groups by sex (male and female), by gestational age (≤26 weeks and >26 weeks), and by respiratory support (invasive ventilation and no invasive ventilation)**. Abbreviations: PDA, patent ductus arteriosus; aOR, adjusted odds ratio; CI, confidence interval. [a]Adjusted for sex, gestational age, small for gestational age, cesarean birth, multiple birth, premature rupture of membranes >24 h, Apgar score at 5 min, use of antenatal steroids, maternal hypertension, Chorioamnionitis, Transport Risk Index of Physiologic Stability score, use of caffeine, invasive ventilation on day 3, number of pulmonary surfactant used within 3 days after birth, inotropes within 3 days after birth, transfusion within 3 days after birth, and early-onset sepsis.

TOLERATE trial. Therefore, rational treatment of PDA in extremely preterm infants may be necessary and practical.

Although our study showed that PDA treatment in extremely preterm infants was associated with decreased mortality, not all infants benefited. The beneficial effect was mainly present among infants who required invasive ventilation. This finding was important because the need for invasive ventilation is the symptom or sign most often considered by clinicians in their decision-making process. This result highlighted the necessity of rational patient selection for PDA treatment. The level of respiratory support may represent the severity of haemodynamic consequences caused by the left-to-right shunting of PDA. Certainly, a judicious haemodynamic assessment of PDA to help select the treatment population would be the best option. However, to date, there is a lack of universally accepted definition of haemodynamically significant PDA and criteria for PDA treatment.[1,32] On the other hand, the fact that invasive ventilation was not required may indicate to some extent that the haemodynamic impact of PDA was not significant. This may explain the lack of benefit from PDA treatment in infants who did not require invasive ventilation as a result of this study. In three randomised controlled trials[9,10,12] evaluating the effects of PDA treatment, 46–75% of the study population was on noninvasive ventilation, which may explain their negative results.

The strengths of our study are the inclusion of a large sample of extremely preterm infants, who had not been adequately represented in previous trials, and the discovery of an interaction between the respiratory status of the infant and the clinical effectiveness of PDA treatment. Our study has some limitations. First, although all PDAs were diagnosed by echocardiography, unfortunately, we did not collect data on ductal haemodynamic indicators, which would be more useful in identifying the target population for treatment. This is mainly due to the fact that high-quality haemodynamic assessment is not widely available in China, reflecting the practical situation of PDA assessment in relatively underdeveloped areas, and secondly due to the current lack of a universally accepted definition of haemodynamically significant PDA. Additionally, the lack of these indicators may result in selection bias. However, previous studies have shown that the proportion of extremely preterm infants with moderate-to-large PDA after the first week of life is approximately two-thirds,[29,33,34] which is consistent with the proportion of extremely preterm infants diagnosed with PDA in this study. Second, the lack of data on ductal haemodynamic indicators may result in treatment selection bias. However, this potential selection bias is likely to tilt the results against treatment rather than in favor of treatment (treatment likely to select larger ducts). Despite inability to account for these confounders, the fact that we found beneficial effects further indicates the robustness of our results. In addition, we found that PDA treatment was beneficial even when the disease severity was higher in the treatment group, again indicating the robustness of our results. Therefore, the association between PDA treatment and decreased mortality does exist. Third, we also lack data on the efficacy of medical treatment, making it difficult to determine whether the beneficial effect of PDA treatment was related to the facilitation of PDA closure. However, the rate of surgical ligation was significantly lower in infants receiving medical treatment than in those who did not, suggesting, in part, that medical treatment was associated with facilitating closure of PDA. Moreover, previous evidence has shown that medical treatment is more effective in closing a PDA than no treatment.[35] Fourth, since there is no guideline for PDA management in China, there may be significant variability in clinical practices, which may bias the results. Finally, despite the fact that we made a rigorous adjustment for confounding factors, unmeasured confounders may still affect our results.

In conclusion, for extremely preterm infants, PDA treatment was associated with a reduction in mortality, but this beneficial effect of PDA treatment on death was mainly present among infants who required invasive ventilation. Further prospective studies with more precise treatment criteria are needed to identify the subgroup of extremely preterm infants who could benefit from PDA treatment.

Contributors

Concept and design: AMQ, SYJ, RC, RY; Acquisition, analysis, or interpretation of data: AMQ, SYJ, XYG, SJL, XPL, WS, JGZ, LYH, TTX, YPZ; Drafting of the manuscript: AMQ, SYJ, RC, RY; Critical revision of the manuscript for important intellectual content: AMQ, SYJ, YC, LZD, WHZ, SKL, RC, RY; Statistical analysis: AMQ, XYG, SJL, XPL, WS; Obtained funding: SKL; Administrative, technical, or material support: YC, LZD, WHZ, SKL; Supervision: YC, LZD, WHZ, SKL, RC, RY. All authors had full access to the data set of the study and had final responsibility for the decision to submit for publication.

Data sharing statement

After the publication of the article, the corresponding author may offer de-identified data, but this requires the provision of scientific rationale and sound methods. Requests for data sharing will be processed according to Chinese Neonatal Network's data sharing policy.

Declaration of interests

The authors have declared no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102356.

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