Systematic Review and Meta-Analysis

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The optimal timing of surgical ligation of patent ductus arteriosus in preterm or very-low-birth-weight infants

A systematic review and meta-analysis

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Abstract

Background: Patent ductus arteriosus (PDA) is a particularly common problem in preterm infants. Although surgical ligation is rarely performed in many contemporary neonatal intensive care units, it remains a necessary treatment option for preterm infants with a large hemodynamically significant PDA under strict clinical criteria, and it can reduce mortality in preterm infants. However, the optimal timing of surgical ligation is still controversial. We conducted this systematic review and meta-analysis to compare the mortality and morbidity of early and late surgical ligation of PDA in preterm or very-low-birth-weight (VLBW) infants.

Methods: This review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42019133686). We searched the databases of PubMed, Embase, the Cochrane Central Register of Controlled Trials, and the World Health Organization International Clinical Trials Registry Platform up to May 2019.

Results: This review included 6 retrospective studies involving 397 premature or VLBW infants with PDA. Pooled analysis showed that compared with the late ligation group, the early ligation group had a lower fraction of inspired oxygen (F_iO_2) at 24 hours postoperatively (mean difference [MD] −6.34, 95% confidence interval [CI] −9.45 to −3.22), fewer intubation days (MD −19.69, 95% CI −29.31 to −10.07), earlier date of full oral feeding (MD −22.98, 95% CI −28.63 to −17.34) and heavier body weight at 36 weeks of conceptional age (MD 232.08, 95% CI 57.28 to 406.88). No significant difference in mortality or other complications was found between the early and late groups.

Conclusion: Our meta-analysis implies that compared with late surgical ligation, early ligation might have a better respiratory outcome and nutritional status for PDA in preterm or VLBW infants. There was no difference in mortality or postoperative complications between early and late ligation. A randomized prospective clinical trial with a possible large sample size is urgently needed to reinvestigate this conclusion.

PROSPERO registration number: CRD42019133686.

Abbreviations: ARDS = acute respiratory distress syndrome, ARF = acute renal failure, BPD = bronchopulmonary dysplasia, BW = body weight, CI = confidence interval, COXi = cyclooxygenase inhibitors, F_iO_2 = fraction of inspired oxygen, GA = gestational age, hsPDA = hemodynamically significant patent ductus arteriosus, IVH = intraventricular hemorrhage, MD = mean difference, MeSH = Medical Subject Headings, NDI = neurodevelopmental impairment, NEC = necrotizing enterocolitis, NICU = neonatal intensive care units, NOS = Newcastle-Ottawa Scale, OR = odds ratio, PDA = patent ductus arteriosus, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, PROSPERO = Prospective Register of Systematic Reviews, ROP = retinopathy of prematurity, VLBW = very-low-birth-weight.

Keywords: meta-analysis, patent ductus arteriosus, preterm infants, surgical ligation

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1. Introduction

The ductus arteriosus in term infants typically closes spontaneously within 3 days after birth. However, it remains open frequently in preterm infants. According to some demographic data, patent ductus arteriosus (PDA) occurs in approximately 46% of preterm infants born at <32 weeks of gestation and in over 70% of preterm infants born at <28 weeks of gestation.[1,2] Although the spontaneous closure rate was high (86%) in untreated preterm infants according to a recent report, the spontaneous closure rate was decreased with lower body weight (BW) or younger gestational age (GA); this rate was significantly lower when BW<1250 g or GA<27+6 weeks.[3]

Persistent ductal shunting results in blood flow from systemic circulation to pulmonary circulation, causing pulmonary hyperemia and systemic hypoperfusion. Pulmonary hyperemia and pulmonary immaturity in preterm neonates lead to subsequent bronchopulmonary dysplasia (BPD) and worse lung conditions. Organ impairments, such as necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), intraventricular hemorrhage (IVH), and acute renal failure (ARF), occur because of systemic hypoperfusion and hypoxia. Finally, mortality increases in premature newborns with PDA compared with those with PDA closure.[4] Under such circumstances, pharmacologic or surgical closure of PDA in preterm infants is scheduled.

Pharmacologic closure using cyclooxygenase inhibitors (COXi) (ibuprofen or indomethacin) is effective for PDA closure in preterm infants. Oral ibuprofen has a high PDA closure rate (84%), associated with a lower risk of grade 3 or 4 IVH, but it increases the risk for oliguria and has no effect on reducing mortality and BPD.[5,6] Indomethacin can also significantly reduce the incidence of symptomatic PDA and shorten the duration of supplemental oxygen, but it does not affect mortality, BPD, IVH, and ROP.[7] However, there is a substantial failure rate of PDA closure after COXi is used more than twice, especially in very-low-birth-weight (VLBW) patients.[8–11] On the other hand, some infants have contraindications for COXi. Without closure, the prolonged and persistent left-to-right shunt in premature infants results in increased morbidity and mortality.[10]

Although surgical ligation is rarely performed in many contemporary neonatal intensive care units (NICUs), it remains a necessary treatment option for preterm infants with a large hemodynamically significant PDA (hsPDA) in whom medical treatment is failed or contraindicated. Under strict clinical criteria and well-performed categorization systems, such as those at The Hospital for Sick Children, Toronto,[12] surgical ligation benefits preterm infants by significantly reducing mortality and not increasing chronic lung disease, ROP, or neurodevelopmental impairment (NDI).[13,14] To date, the timing of surgical ligation of PDA in preterm infants remains controversial. Many reports have shown that early ligation (less than 2 or 3 weeks of life) benefited preterm infants with a lower incidence of BPD and NEC, improved enteral feeding tolerance, and shortened the delay for full oral feeding.[15–18] Nonetheless, the study by Sung SI indicated that delayed surgical ligation for PDA in extremely preterm infants was associated with decreased mortality or morbidity.[19] Here, we systematically reviewed and meta-analyzed all the included studies to compare the mortality and morbidity of early and late surgical ligation of PDA in preterm or VLBW infants.

2. Material and methods

2.1. Study protocol

This review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (CRD 42019133686). We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement to conduct this systemic review and meta-analysis. Because this was systematic literature research, ethical approval was waived.

2.2. Search strategy

We searched PubMed, Embase, the Cochrane Central Register of Controlled Trials, and World Health Organization International Clinical Trials Registry Platform using the following Medical Subject Headings (MeSH) terms: “infant, premature”, “premature birth”, “infant, very low birth weight”, “infant, newborn”, “ductus arteriosus, patent”, “surgical procedures, operative”, “ligation”, and the related keywords. The search was updated to May 2019.

2.3. Study selection

We included all the studies satisfying the following criteria:

1. Participants: preterm infants <37 weeks gestational age or body weight <1500 g with a PDA diagnosed clinically or by echocardiography in the neonatal period;
2. Interventions: early surgical ligation;
3. Comparison: late surgical ligation (the cut-off time of early and late ligation was 2 weeks or 3 weeks of life; we included studies that involved patients who underwent surgical ligation because of drug treatment failure or drug contraindications, regardless of the dose or courses of drug treatment before surgery);
4. Outcomes: the primary outcome was the mortality of each group.

Three secondary outcomes were examined:

1. Respiratory data: fraction of inspired oxygen (F_iO_2) at 24 hours postoperatively, intubation days and BPD (defined as the need for oxygen or positive-pressure support at 36 weeks of conceptional age[20]);
2. Nutritional status: date of full oral feeding and body weight at 36 weeks of conceptional age;
3. Postoperative complications: NEC (met the criteria for grade II or higher using Bell staging criteria[21]), severe ROP (stage ≥3, defined and classified according to the International Classification of Diseases for ROP[22]), ARF (creatinine>1.7 mg/dl), severe IVH (grade III or IV, classified using Volpe’s grading system[23]) and hospital stay.

The exclusion criteria for the study were as follows:

1. studies of infants with other acute congenital structural heart diseases;
2. studies that did not contain early and late ligation groups;
3. studies containing early and late groups but with a significant difference in the preoperative baseline characteristics or the percentage of infants with acute respiratory distress syndrome (ARDS), resuscitation at birth and pulmonary hemorrhage before surgery.

2.4. Data collection and quality assessment

Two investigators (Hualin Yan, Fan Ma) independently assessed the eligibility of reports at the title and abstract level, and a third reviewer (Yifei Li) determined the divergences together; studies that met the inclusion criteria were selected for further analysis.

We used the Newcastle–Ottawa Scale (NOS) for quality assessment.[24]

2.5. Data synthesis and data analysis

We used Review Manager version 5.3 and STATA version 14 for data synthesis and data analysis. Mortality, BPD, NEC, severe ROP, ARF, and severe IVH were calculated as odds ratios (ORs). F_iO_2 at 24 hours postoperatively, intubation days, date of full oral feeding, body weight at 36 weeks, and hospital stay of each study were calculated as mean differences (MDs). When there were only median and range data in the literature, we used the formulas from Hozo SP to estimate the mean and standard deviation.[25] A fixed-effects model was used for analyses when heterogeneity was not present ($P > .05$). Otherwise, a random-effects model was used.

We used Egger test to evaluate the potential publication bias by STATA 14.0, and $P < .05$ was considered to indicate significant publication bias.[26] The Chi-Squared test and *I*-square test were used to detect study heterogeneity. Heterogeneity was considered significant when $P < .10$ or $I^2 > 50\%$. When heterogeneity was present, we conducted a meta-regression to determine the source of heterogeneity. To assess the robustness of the pooled results, we conducted sensitivity analysis for all studies.

3. Results

3.1. Study evaluation

We selected 30 studies for full-text review after title and abstract screening. After the full-text review, 24 citations were excluded according to the selection criteria, and 6 remaining articles underwent further quality assessment and data extraction (Fig. 1).[15–18,27,28] The Newcastle–Ottawa Scale (NOS) of each study was at least 7 points to ensure the study quality (Table 1; see Table, Supplemental Digital Content 1, http://links.lww.com/MD/D875, which indicates the detailed NOS scores). These 6 articles were ultimately involved in this review.[15–18,27,28]

3.2. Study characteristics

The main characteristics of the 6 included studies are reported in Table 1. They were all retrospective studies involving 397

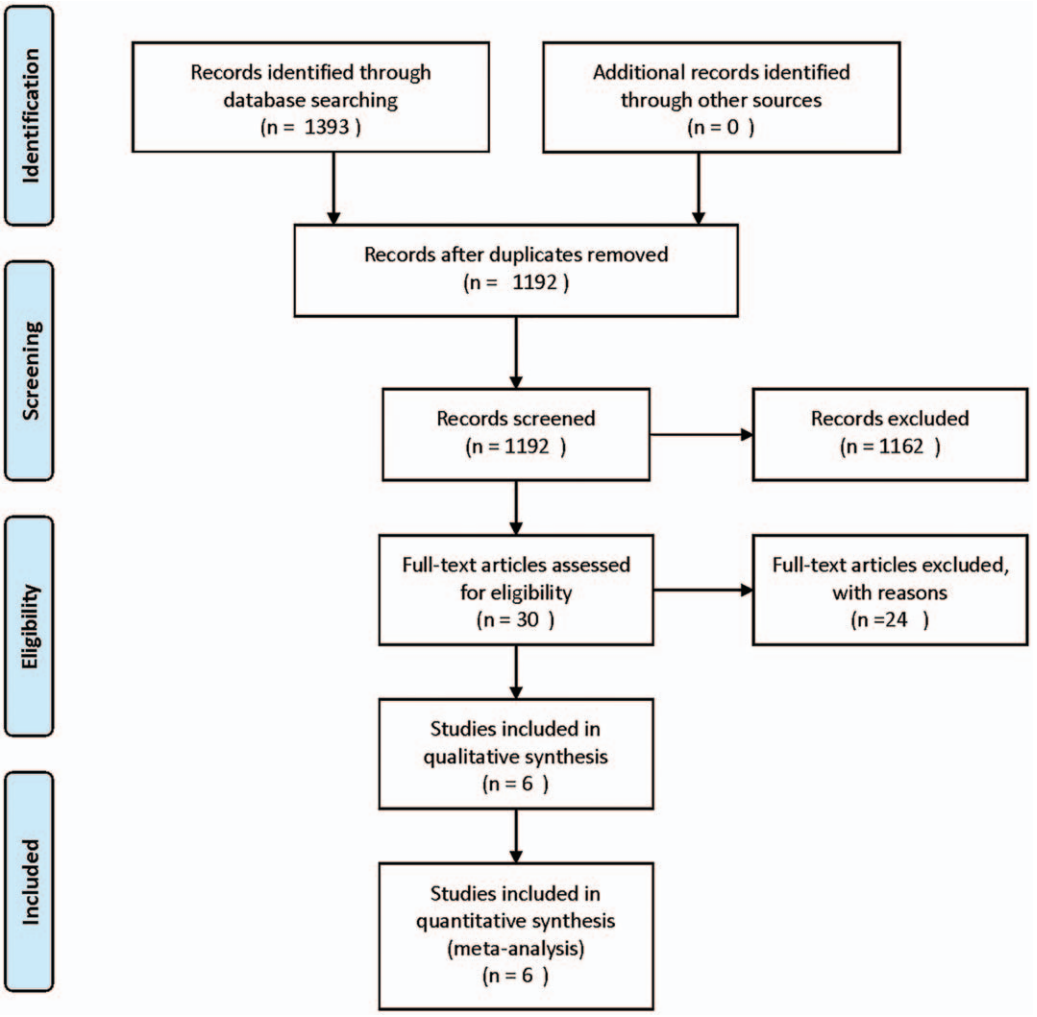

Figure 1. Flow diagram of the study selection process.

Table 1

Main characteristics of included studies.

Author, year	Partici-pants	mean GA (weeks)	mean BW (g)	Age at surgery (day)	Patent ductus size (mm)	Left atrial/ aortic diameter	Treatment (early ligation time)	No. of treat patients	control treatment (late ligation time)	No. of control patients	NOS scores
Jaillard, S., 2006	58	26	809(530-1240)	EL:15.5 LL:30	N/A	2	≤21 days	30	>21 days	28	9
Ibrahim, M. H.,2015	120	24.9	768(607-901)	EL:12 LL:30	N/A	2.0	≤3 weeks	75	>3 weeks	45	9
Fonseca, E., 2014	41	26	930(510-1500)	EL:<21 LL:>21	N/A	N/A	≤21 days	14	>21 days	27	8
Hsiao, C. C, 2009	56	25.2	709(430-1310)	EL:11.2 LL:20.3	N/A	N/A	≤ 14 days	13	> 14 days	43	8
Lee, J. H., 2014	64	26.3	846(629-1073)	EL:10.2 LL:24.5	2.3	1.5	≤ 15 days	28	> 15 days	36	7
Youn, Y., 2017	58	27.3	1043±270	EL:9.2 LL: 30.8	N/A	N/A	≤2 weeks	29	≥2 weeks	29	7

BW = birth weight, EL = early ligation, GA = gestational age, LL = late ligation, NOS = Newcastle-Ottawa Scale, N/A = not applicable.

premature or VLBW infants with PDA. The mean gestational age ranged from 24.9 weeks to 27.3 weeks, and the mean birth weight ranged from 709 g to 1043 g. Only the study by Lee, J. H. (2014) reported the average patent ductus size of patients (2.3 mm, Table 1), and the studies by Jaillard, S.(2006), Ibrahim, M. H. (2015), and Lee, J. H. (2014) recorded the ratio of the size of the left atrium to the diameter of the aortic root (2, 2.0, 1.5, respectively, Table 1). There was no significant difference in these basic characteristics between the early and late ligation groups in each study.

3.3. Mortality

The results of the primary outcome are listed in Figure 2. No significant difference in mortality was found between the groups ($P=.09$, Fig. 2), and no significant heterogeneity was detected by the Chi-Squared test or *I*-square test ($P=.87$, $I^2=0\%$, Fig. 2).

3.4. Secondary outcomes

For respiratory outcomes, the early ligation group needed a lower F_iO_2 at 24 hours postoperatively (mean difference [MD] −6.34, 95% CI −9.45 to −3.22, $P<.0001$, Fig. 3A) and fewer intubation days than the late ligation controls (MD −19.69, 95% CI −29.31 to −10.07, $P<.0001$, Fig. 3B). However, the incidence of BPD was not significantly different between the early and late groups ($P=.09$, Fig. 3C). No significant heterogeneity was detected by the Chi-Squared test or *I*-square test of F_iO_2 ($P=.77$, $I^2=0\%$, Fig. 3A) and BPD ($P=.20$, $I^2=34\%$, Fig. 3C). There was significant heterogeneity in the pooled result of intubation days ($P<.00001$, $I^2=92\%$, Fig. 3B), so the pooled result of intubation days should be interpreted with caution.

The nutritional status of the early group was better than that of the late group. The early group had an earlier date of full oral feeding (MD −22.98, 95% CI −28.63 to −17.34, $P<.00001$, Fig. 4A) and heavier body weight at 36 weeks of conceptional age (MD 232.08, 95% CI 57.28 to 406.88, $P=.009$, Fig. 4B). No significant heterogeneity in the date of full oral feeding was detected ($P=.55$, $I^2=0\%$, Fig. 4A). There was significant heterogeneity in the pooled result of body weight at 36 weeks of conceptional age ($P=.06$, $I^2=73\%$, Fig. 4B), so we should draw this conclusion carefully.

There was no significant difference in the postoperative complication rate between the 2 groups, which included NEC, severe ROP, ARF, severe IVH, and hospital stay (Fig. 5). No significant heterogeneity was detected in NEC, severe ROP, or hospital stay. There was significant heterogeneity in the pooled results of ARF ($P=.04$, $I^2=77\%$, Fig. 5C) and severe IVH ($P=.03$, $I^2=71\%$, Fig. 5D), so the overall results of ARF and severe IVH should be interpreted with caution.

3.5. Quality and bias assessment

Egger test did not detect any publication bias for the outcomes (see Figure, Supplemental Digital Content 2, http://links.lww.

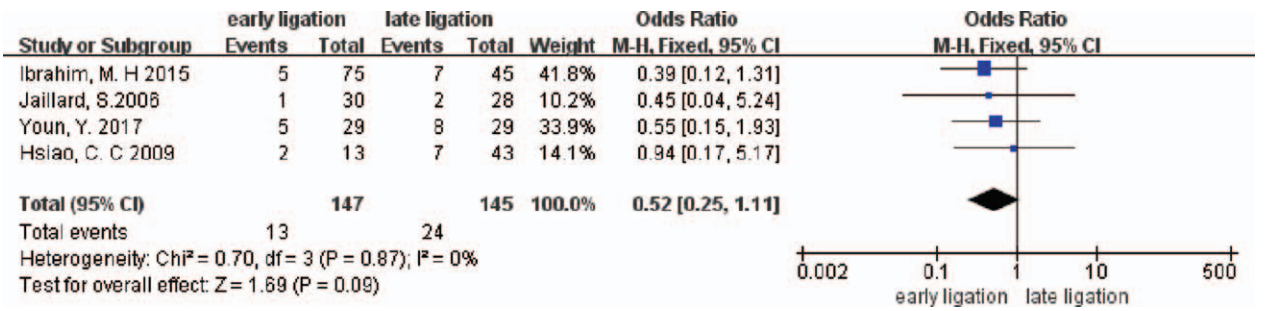

Figure 2. Primary outcome: Forest plot for the comparison of mortality between early ligation and late ligation. CI, confidence interval; df, degrees of freedom.

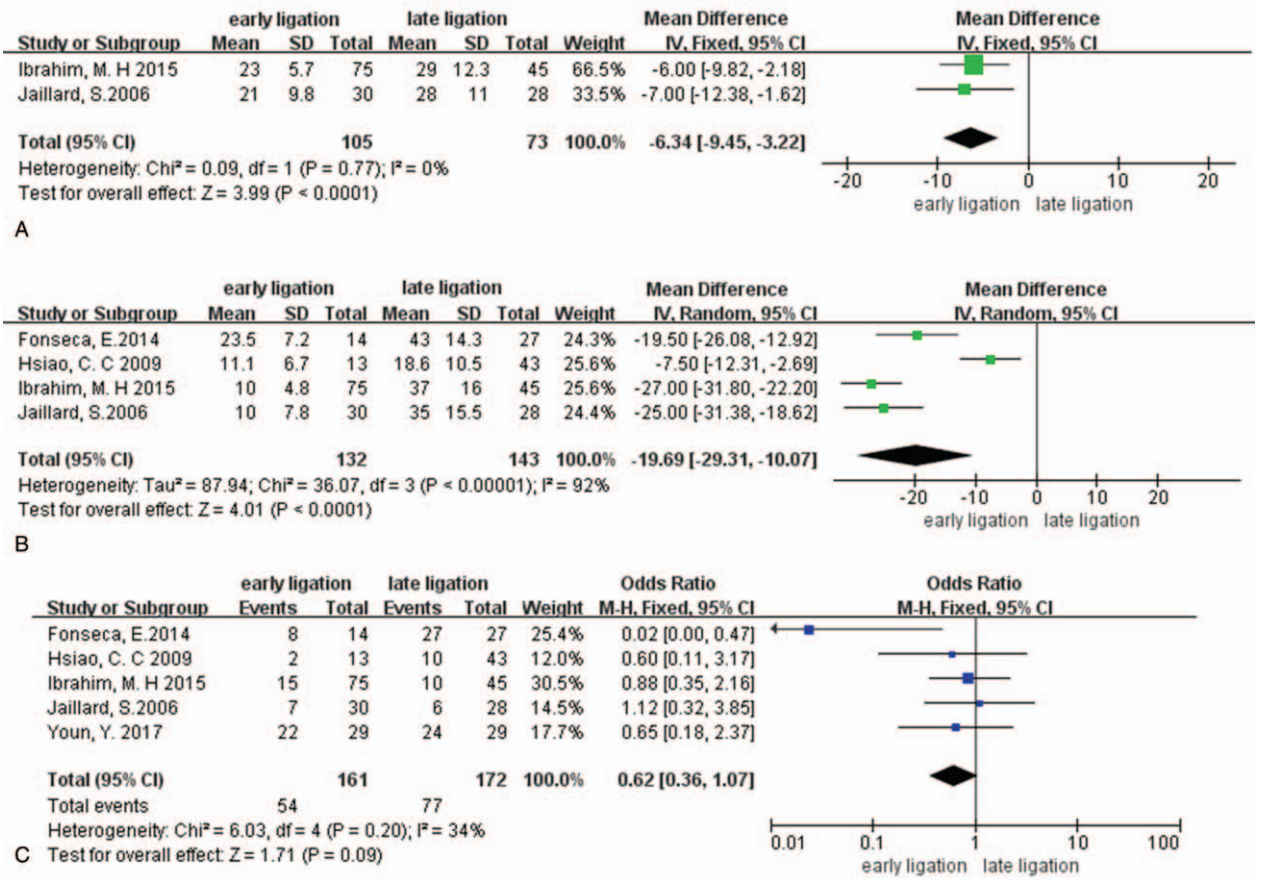

Figure 3. Secondary outcomes: 1: Forest plot for the comparison of respiratory outcomes between early ligation and late ligation. (A) F_iO_2 at 24 hours postoperatively, (B) intubation days, (C) BPD. BPD, bronchopulmonary dysplasia; CI, confidence interval; df, degrees of freedom; F_iO_2, fraction of inspired oxygen; SD, standard deviation.

com/MD/D876 which demonstrates Egger funnel plots of outcomes).

The meta-regression analysis showed that publication year, total patients, mean gestational age, mean birth weight, NOS scores, and different cut-off times (2 weeks or 3 weeks) were not potential sources of heterogeneity for intubation days and severe IVH outcomes (see Figure, Supplemental Digital Content 3, http://links.lww.com/MD/D877 which demonstrates the meta-regression results). Due to limited observations, meta-regression analysis could not be performed for the

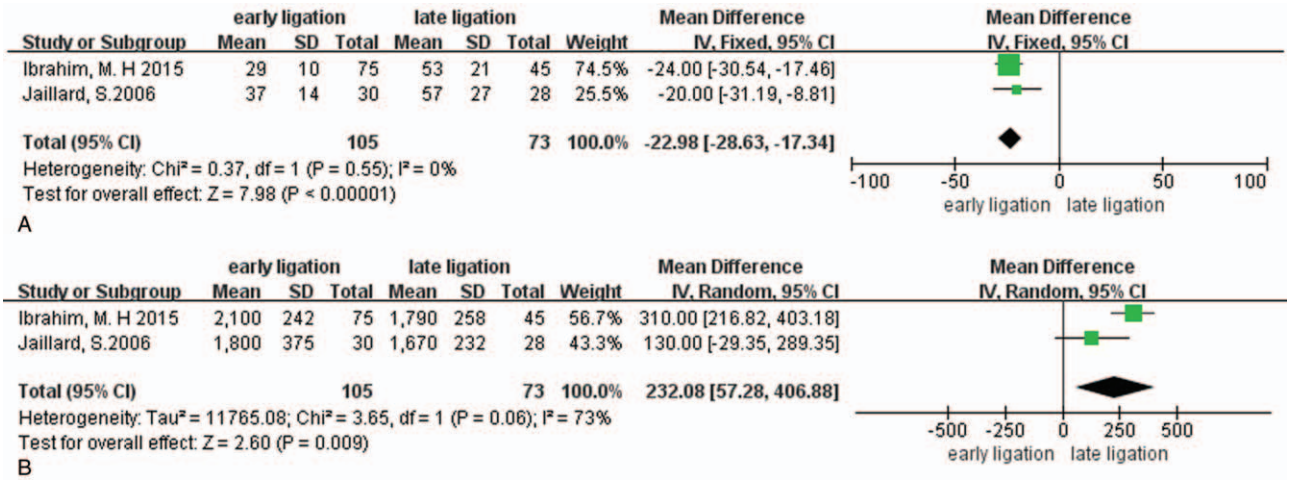

Figure 4. Secondary outcomes 2: Forest plot for the comparison of nutritional outcomes between early ligation and late ligation. (A) date of full oral feeding, (B) body weight at 36 weeks of conceptional age. CI, confidence interval; df, degrees of freedom; SD, standard deviation.

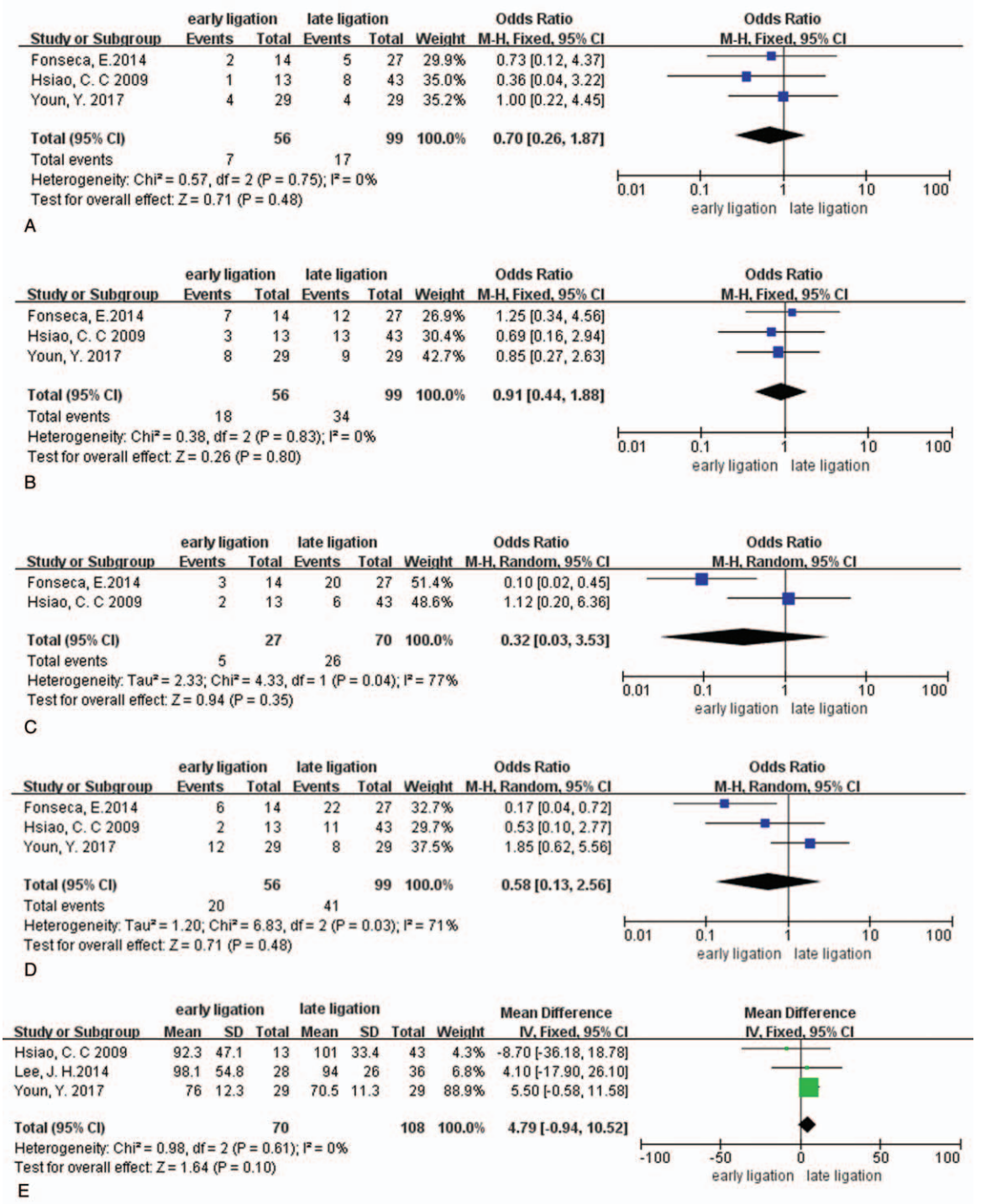

Figure 5. Secondary outcomes 3: Forest plot for the comparison of postoperative complications between early ligation and late ligation. (A) NEC, (B) severe ROP, (C) ARF, (D) severe IVH, and (E) hospital stay. ARF, acute renal failure; CI, confidence interval; df, degrees of freedom; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity; SD, standard deviation.

outcomes of ARF and body weight at 36 weeks of conceptional age.

When the sensitivity analysis was conducted, all the outcomes were stable except for IVH. Sensitivity analysis revealed that the study by Youn, Y. (2017) was the main source of heterogeneity (Table 2).

4. Discussion

Over the past several decades, the benefit and risk of surgical ligation for PDA in preterm infants have always been in dispute. Several observational studies and a meta-analysis have demonstrated that surgical ligation is associated with increased BPD, severe ROP, and NDI.[13,29–31] However, there were potential

Table 2

Sensitivity analysis of early and late groups in severe IVH.

Removed Study	Pooled result		Study heterogeneity	
	Odds ratio	*P* value	I^2	*P* value
Fonseca, E.,	1.16(0.35, 3.82)	.81	35%	.22
Hsiao, C. C,	0.59 (0.06, 6.09)	.66	85%	.01
Youn, Y.,	0.28 (0.09, 0.84)	.02	3%	.31

IVH = intraventricular hemorrhage.

residual biases in previous observational studies that threatened the validity of these studies.[32] A recent cohort study with minimized residual bias showed that PDA ligation among preterm neonates was not associated with BPD, ROP or NDI among survivors.[14] The reported mortality of surgical ligation for premature infants was approximately 7.8% to 10.7%.[30,33–35] Compared with pharmacologic treatment, surgical ligation significantly reduced mortality in preterm infants.[13,14] Perhaps this debate will continue until solid evidence from the large-sample randomized clinical trial is provided.

On the other hand, surgical ligation for PDA in preterm infants is rarely performed in contemporary NICUs and is partly replaced by percutaneous closure for suitable patients. NICU management decreased the rates of COXi use or ligation with decreasing related BPD or death.[36] There was evidence that percutaneous PDA closure was safe and feasible, was associated with few adverse events and could improve the respiratory status, even in very preterm infants.[37,38] Nevertheless, the procedure-related complications (vascular injuries and device embolization) were significantly higher for device closure compared with surgical ligation;[39] sufficient body weight (>3 kg) was needed to ensure the safety of this procedure,[40] and economic evaluations alongside clinical trials were necessary because of the high cost. Hence, before the randomized clinical trials and stronger evidence argue for its validity, the appropriate patient selection and the optimal timing for percutaneous closure in preterm or VLBW infants remain controversial. Therefore, for VLBW premature infants with a large hsPDA in whom medical treatment is contraindicated or has failed, surgical ligation remains a necessary treatment option with no worse complications and with lower mortality under strict clinical criteria and a well-performed categorization system, such as those at The Hospital for Sick Children, Toronto.[12]

Therefore, the decision for the optimal timing of surgical closure for suitable patients is essential. For the first time, this systemic review meta-analyzed the outcomes of early and late surgical ligation of PDA in preterm or VLBW infants. We aim to obtain a clearer answer to the debate of early or late ligation.

Our results showed that compared with late surgical ligation, early surgical ligation might have a better respiratory outcome (lower FiO_2 at 24 hours postoperatively and fewer intubation days) and nutritional status (earlier date of full oral feeding and heavier body weight at 36 weeks) for PDA in preterm or VLBW infants. This conclusion was consistent with those of previous individual studies.[15–17] Prolonged exposure to ductus arteriosus shunting, which means a longer duration of pulmonary hyperemia and systemic hypoperfusion, can cause worse lung conditions and lead to poorer nutritional status in late ligation.[10] In addition, longer exposure of hsPDA and mechanical ventilation were associated with worse neuro-developmental outcomes,[41] which was in line with the results from the study by Fonseca, E. and colleagues that early ligation improved neurological outcomes.[18] However, no significant difference in mortality and postoperative complications was found between the early and late groups in our analysis results, in accordance with the results from the study by Youn, Y. and colleagues.[28] Therefore, the benefit of early ligation should be reinvestigated with more convincing evidence given the lack of differences in mortality and postoperative complications.

The study by Sung SI concluded that delayed surgical ligation was associated with decreased mortality or morbidities.[42] However, there were 2 distinct differences between our research and that of Sung SI. First, the grouping of Sung SI into early and late ligation was intentional. Sung SI used contraindications of pharmacologic treatment as a primary ligation group and failure after pharmacologic treatment as a secondary ligation group. The late group received combined treatment, while the early group received only surgery. Second, the population in the study by Sung SI narrowed to 23–25 weeks extremely preterm infants. These may be the reasons why we reached a different conclusion.

Truly, it is difficult to give a strong recommendation for the optimal timing of surgical ligation of PDA in preterm or VLBW infants because of the following limitations. First, we only included 6 retrospective observational studies with a small sample size, which lowered the level of evidence. However, it is difficult to conduct a prospective randomized clinical trial due to surgical procedures and ethical concerns. A well-designed trial and large sample size can also upgrade the evidence level. Second, although meta-regression analysis did not detect publication year and mean birth weight as potential confounders, preterm infants with mean birth weight of 400–749 g had significantly different outcome responses to PDA ligation, and the publication period from 2008 to 2015 showed varied PDA ligation outcomes among preterm infants in the NICU.[36] In our included studies, the mean birth weight was from 709 g to 1043 g, and the publication period was from 2006 to 2017, which indicates the presence of potential confounding factors and heterogeneity of outcomes. Third, there were 4 pooled outcomes with significant heterogeneity that were confounders of the pooled results. The inclusion of a larger number of more recent studies with large sample sizes would partly solve this problem. Last, only 3 studies reported the patent ductus size and left atrial/aortic diameter ratio, which are important baseline parameters for patients with PDA preoperatively and may affect the analysis results.

In conclusion, our review implied that compared with late surgical ligation, early ligation might have a better respiratory outcome and nutritional status for PDA in preterm or VLBW infants. There was no difference in mortality or postoperative complications between early and late ligation. A randomized prospective clinical trial with a possible large sample size is urgently needed to confirm this conclusion.

Author contributions

Conceptualization: Hualin Yan, Chaomin Wan.
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Supervision: Yimin Hua, Chaomin Wan.

Validation: Yifei Li.
Writing – original draft: Hualin Yan.
Writing – review & editing: Hualin Yan, Fan Ma, Chaomin Wan.

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