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REVIEW

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# Sildenafil for pulmonary hypertension in neonates: An updated systematic review and meta-analysis

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## Abstract

**Objectives:** To provide an updated review and meta-analysis on the efficacy and safety of sildenafil for treating persistent pulmonary hypertension in neonates (PPHN).

**Methods:** PubMed/Medline, SCOPUS, Cochrane Central Register of Controlled Trials, and Web of Science were searched from the inception of publication to January 2021. The principal outcomes include oxygenation parameters, hemodynamic metrics and echocardiographic measurements, as well as adverse outcomes.

**Results:** A total of eight studies were included with 216 term and premature neonates with PPHN. Compelling evidence showed the use of sildenafil could improve the prognosis of PPHN neonates, compared with baseline or placebo in neonates with PPHN, and a time-dependent pattern of the improvements can be observed. After 24 h of treatment, the Oxygenation index suggested a steady decrease (*SD*: −1.80, 95% confidence interval [CI]: −2.92, −0.67) and sildenafil exerted peak effects after 72 h of treatment (*SD*: −4.02, 95% CI: −5.45, −2.59). No clinically significant side effects were identified. Egger's test and funnel plots of the major outcomes were performed, and the publication bias was not significant.

**Conclusion:** Improvements were shown in oxygenation index, pulmonary arterial pressure, and adverse outcomes after using sildenafil for PPHN in neonates. However, future research with robust longitudinal or randomized controlled design is still needed.

KEYWORDS

Pulmonary hypertension in neonates, sildenafil, systemic review and meta-analysis

## 1 | INTRODUCTION

When the pulmonary circulation of a neonate fails to adapt to extrauterine life due to pulmonary or systemic conditions, persistent pulmonary hypertension of the newborn (PPHN) may occur, leading to acute respiratory failure.[1] Newborns with PPHN may manifest with sustained elevation of pulmonary vascular resistance, decreased perfusion of the lungs, and continued right-to-left shunting of blood through foramen ovale and ductus arteriosus.[2–4] Clinically, the diagnosis of PPHN can be confirmed when the partial pressure of oxygen in arterial blood ($PaO_2$) is less than 55 mmHg despite a fraction of inspired oxygen ($FiO_2$) of 1.0 or when a preductal to

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postductal oxygen gradient is greater than 20 mmHg.[5,6] PPHN affects up to 2–6 per 1000 live births; this accounts for approximately 10% of all infants admitted to the neonatal intensive care (NICU), and is responsible for up to 8%–10% of death and 25% of long-term neurodevelopmental morbidity of neonates.[7–9] PPHN is usually associated with poor outcomes, which may be due to its heterogeneous etiology and the limited interventions.[7–9]

The difficult management of PPHN is a result of its complex etiologies and risk factors. The Nice World Symposium classification of PH has classified the PPHN as a separate subcategory in the group 1 "pulmonary arterial hypertension."[10,11] Studies have clinically classified PPHN into three categories: (1) the abnormally constricted pulmonary vasculature, which is the most common type, consisting of, meconium aspiration syndrome (MAS), pulmonary arterial thrombosis, respiratory distress syndrome, and neonatal sepsis or thyrotoxicosis; (2) the structurally abnormal vasculature, which is often termed idiopathic PPHN, including congenital cardiac defects and premature intrauterine constriction of the ductus arteriosus; or (3) the hypoplastic vasculature seen in congenital diaphragmatic hernia or alveolar capillary dysplasia, a rare malformation of lung development.[8,12] So far, studies have reported various risk factors attributable to the onset of PPHN, namely, cesarean delivery, MAS, severe respiratory distress due to primary surfactant deficiency in the preterm infant, neonatal infection, and sepsis, as well as poorer socioeconomic conditions.[11,13–15] Scholars have also noted distinct disparities in adverse neonatal outcomes in high-income countries versus low-middle income countries.[13-15]

Currently, the therapeutic mainstay for PPHN involves mechanical ventilation and administration of inhaled nitric oxide (iNO), which can help dilate the pulmonary vasculature; however, iNO is expensive and not easily accessible, especially in rural areas, and approximately 30%–40% of patients failed to respond to iNO or did not experience improved oxygenation.[2] Therefore, alternatives are needed, and some novel modalities of treatments have emerged, including systemic and inhaled vasodilators (namely, prostaglandin E1, prostacyclin), endothelin antagonists (namely, iloprost[16,17] and treprostinil[18]), and phosphodiesterase type 5 (PDE5) inhibitors (namely, sildenafil[19,20]). Among these potential drugs, sildenafil is widely used in underdeveloped countries as a substitute for iNO.[21] Sildenafil citrate prevents PDE5 from degrading cyclic guanosine monophosphate (cGMP), thus increasing cGMP level and enhancing NO-mediated vasodilation.[22]

In 1999, the first use of sildenafil in infants was reported, which has been shown to facilitate weaning from iNO after corrective cardiac surgery.[23] During the past decade, there has been increasing interest in the off-label use of sildenafil for treating PH of various etiologies in term and premature infants with PPHN and bronchopulmonary dysplasia (BPD) despite a lack of guidelines to support its use.[24] In 2019, Marisa et al. reported that sildenafil may be associated with improvement in BPD-associated pulmonary hypertension and respiratory scores in preterm infants.[25]

However, recent data led to concerns about the safety of PDE5 inhibitors in children, where a clinical trial showed a higher risk of mortality after 2 years of treatment among pediatric patients receiving high-dose versus low-dose sildenafil.[26] As a result, the Food and Drug Administration (FDA) in the United States issued a safety advisory against the use of sildenafil in pediatric patients (aged 1 to 17 years old) in 2012.[2,27] However, the FDA in the United States did not mention the risks of sildenafil use in neonates, especially in premature neonates.

Some meta-analyses advocated the efficacy of sildenafil use in neonates, suggesting that sildenafil may substitute iNO in rescuing term and preterm neonates with PPHN, especially in resource-limited areas.[2,28–30] However, limitations still exist regarding the meta-analyses currently available. Krystle et al. and Unegbu et al. performed a systematic review respectively in 2015 and in 2017, but neither of them analyze the pooled effects quantitatively.[2,28] Gao et al. performed a network meta-analysis on the drugs for pulmonary arterial hypertension, yet they did not provide insights into the efficacy and safety of PED5 inhibitors on neonates.[29] In 2017, Kelly et al. performed a meta-analysis on the effects of sildenafil on treating PPHN versus both placebo and active therapies, where the authors also investigated the combined effects of sildenafil with iNO in treating PPHN.[30]

Therefore, considering the currently limited information concerning the clinical use of sildenafil, we aimed to conduct an updated meta-analysis on the current evidence of the efficacy and safety of sildenafil in neonates with PPHN. To provide comprehensive, robust, and reliable guidance for clinical use, we recruited all kinds of the original study, including randomized controlled trials (RCT), quasi-randomized trials, and nonrandomized studies on the use of sildenafil in treating PPHN, regardless of the use of iNO or mechanical ventilation.

## 2 | METHODS

### 2.1 | Search methods for identification of studies

A systematic search of the literature was performed using MEDLINE/PubMed, Scopus, and Cochrane Library, from the inception of the database through January 2021. Filters were used to maximize original research, with limitations set to exclude reviews, editorials, or errata as possible. A clinical pediatrician and neonatologist (Shasha Han) scrutinized the search strategy by narrowing and selecting the appropriate search terms. The search terms used were presented in Annex 1. Previous reviews and bibliographic citations of relevant publications were examined to elicit any missing studies. The searches and studies included were limited by subject species (Human) but not by publication date or language (English).

### 2.2 | Inclusion criteria

#### 2.2.1 | Types of studies

We included RCT, quasi-RCT, and nonrandomized observational studies regardless of year of publication for inclusion eligibility.

### 2.2.2 | Types of participants

We included both term and preterm infants (≤28 days old) with PPHN who were exposed to sildenafil during their initial hospitalization. We included studies in which the diagnosis was based on clinical findings with or without echocardiographic confirmation.

### 2.2.3 | Types of interventions

Studies were included if sildenafil was evaluated in comparison with placebos or other pulmonary vasodilators in neonates with PPHN, irrespective of dose, route, and duration of administration.

### 2.2.4 | Types of outcome measures

Studies were included if they included the following outcomes:

- Hemodynamic parameters, both absolute values and mean changes from baseline measured after the first dose, and other timepoints of treatment, including pulmonary arterial pressure (PAP) in mmHg, blood gas tension ($PaO_2$, $PaCO_2$), and mean arterial blood pressure in mmHg;
- Pulmonary-related parameters, including alveolar-arterial oxygen difference (A-a $DO_2$), mean airway pressure;
- Oxygenation index (OI = mean airway pressure ($cmH_2O$) × $FiO_2$ × 100/$PaO_2$ (mmHg)), both absolute values and mean changes from baseline measured after first dose, and other timepoints of treatment;
- Echocardiographic parameters including the systolic and diastolic right ventricular tissue doppler imaging (TDI) myocardial velocities, right ventricular systolic pressure (RVSP) (mmHg) and right ventricular outflow (RVO) (ml/kg/min);
- All-cause mortality within the first 28 days of age (neonatal mortality);
- Any clinically important adverse effects, including retinopathy, epistaxis, headache, dyspepsia, and intraventricular hemorrhage, and so on;
- Length of hospitalization (days) and other clinically important outcomes having not prespecified.

### 2.2.5 | Exclusion criteria

1) Studies were excluded if data on the neonates (<28days) cannot be extracted, or the subjects were mixed with other population;
2) Studies that recruited patients with known structural heart disease (other than patent foramen ovale or patent ductus arteriosus);
3) Studies reporting nonhuman subjects;
4) Studies written in languages other than English;
5) Case report, case series, case review, and cross-sectional studies were excluded.

### 2.2.6 | Data collection and analysis

Two independent reviewers (Kai Zhou and Zonglin He) determined the inclusion for full-text review of abstracts and titles obtained by the search. When disagreement arose, a third reviewer (Sui Zhu) assessed the eligibility and consensus would be made. Eligible studies as determined by the full-text review were included in the systematic review. The publication year, author, demographic characteristics of the subjects, quality of the study, research design, analysis, and results were abstracted from included studies. We extracted data on the following outcomes: Hemodynamic parameters, all-cause mortality, oxygenation index, length of hospitalization (days), any clinically important adverse outcomes, alveolar-arterial oxygen difference (A-a $DO_2$), etc. The quality of the RCTs included in our systematic review was assessed using the Cochrane scale and the Newcastle-Ottawa quality assessment scale was used for the observational studies.[31,32] The Newcastle-Ottawa and Cochrane scale have been utilized to improve the transparency and the completeness of reporting of observational and experimental studies, respectively, and to assess the content of scientific articles (introduction, methods, results, discussion). All discrepancies were resolved through consensus.

### 2.2.7 | Statistical analysis

Statistical analysis was performed using the Stata version 14.0 statistical software (Stata Corp LP). In the primary analysis, heterogeneity among the studies was analyzed with the Cochran *Q* statistic and unexplained interstudy heterogeneity ($I^2$ index) is reported. Significant substantial heterogeneity is considered if $I^2$ is greater than 50%, and thus random-effects model was applied; otherwise fixed-effects model would be used.[33,34] The analyses were based on study types, and the etiologies of PPHN to reduce the heterogeneity. To assess for publication bias, we performed the funnel plot and Begg and Egger's test for evidence of small study effects.[35] Categorical outcomes were reported as risk ratio (RR), and continuous outcome was reported as mean and standard difference (SD), with their corresponding 95% confidence intervals (CIs). To trace the source of the heterogeneity, we also performed subgroup analyses regarding the study design, treatment duration and several types of control. We also further performed the sensitivity analysis to trace the source of heterogeneity by excluding the pooled studies one by one. Specifically, as multiple time points of the effects were reported in the original studies and collected, we combined all the results in the same meta-analytic analyses to better present the time-dependent pattern of the effects instead of generating the combined effects, considering the small number of studies in each category.

However, combined effects were targeted and presented for estimates like mortality and adverse outcomes.

## 3 | RESULTS

### 3.1 | Study characteristics

In this updated meta-analysis, a total of 1286 citations were retrieved (Figure 1), and after reviewed titles and abstracts, eight eligible studies satisfied the inclusion and exclusion criteria and were enrolled for quantitative analysis, with 216 neonates pooled. A total of three cohort studies and five RCT studies investigating the comparison of the use of sildenafil against placebo were included. The studies were mainly conducted in resource-limited countries such as Columbia, Mexico, Qatar, and Egypt. This meta-analysis evaluated the comparisons of sildenafil against placebo. The characteristics of the studies included were presented in Table 1.

### 3.2 | Hemodynamic and pulmonary parameters

#### 3.2.1 | Mean airway pressure

Two RCT studies evaluating sildenafil reported the mean airway pressure,[36,37] and the meta-analyses showed a time-dependent pattern preferring sildenafil use, which greatly decreased mean pulmonary airway pressure 72 h after treatment (SMD: −3.92, 95% CI: −5.32, −2.51), as shown in Table 2 and Figure 2.

#### 3.2.2 | Mean pulmonary arterial blood pressure (mmHg)

Two RCT studies[37,38] reported the mean PAP, as shown in Table 2. Differences were readily discernible between sildenafil and placebo (*SD*: 0.45, 95% CI: −0.11, 1.02; $I^2$ = 83.7%). After 24 h of the treatment, the effects of sildenafil were the most obvious, and the mean arterial pressure was significantly decreased (SMD: −3.13, 95% CI: −4.83, −1.42; $I^2$ = not applicable), though the 95% CI crossed the null hypothesis.

#### 3.2.3 | Partial pressure of $O_2$

Three RCT studies reported the partial pressure of $O_2$ as shown in Table 2, where at the baseline, after the first dose and 6–7 h of treatment, no obvious differences between the sildenafil and the control group were found, as all their 95% CI crossed the null hypothesis. But after 72 h of treatment, sildenafil significantly elevated the $PaO_2$ levels versus the placebo (SMD: 2.84, 95% CI: 2.08, 3.60; $I^2$ = inapplicable). Moreover, a time-dependent pattern can be obviously discerned, and sildenafil use was favored.

#### 3.2.4 | A-a $O_2$ difference

Two RCT studies reported A-a $O_2$ difference,[36,37] and a time-dependent pattern of the effects on the A-a $O_2$ difference was observed as shown in Table 2. There was no significant difference at the baseline and after 24 h of treatment. However, sildenafil

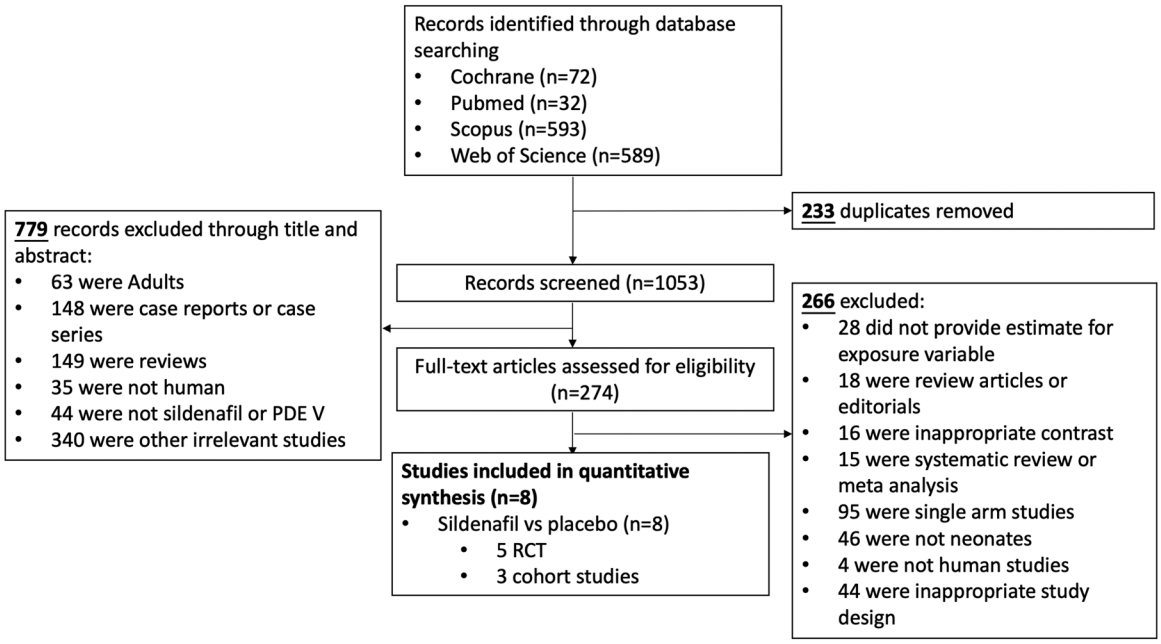


**FIGURE 1** Flow chart of study selection

**TABLE 1** The characteristics of the included studies

| Study | Design | Country | Patients | Age | Birth weight | Total number | PPHN Type | PPHN diagnosis | Intervention | Route | Use of iNO |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Al Omar et al. (2016) | RCT | Qatar | Pre-term and term neonates | >34 g.w. and <48 h p.a. | Sildenafil group 3107 ± 7 g; control group 3179 ± 627 g | 24 | Idiopathic | Echocardiographically confirmed (presence of right-to-left shunt and estimated PAP ≥ 40) | Oral sildenafil or placebo (Saline); Oral sildenafil: 2 mg/kg Q6h | oral | All patients used iNO |
| Baquero et al. (2006) | RCT | Colombia | Term and near-term | ≥35.5 g.w. and <3d p.a. | Sildenafil group 2803 ± 617 g; control group 2710 ± 554 g | 13 | Idiopathic | Echocardiographically confirmed (presence of right-to-left shunt and estimated PAP ≥ 40) | Oral sildenafil or placebo (diluent). | oral | No facility available to administer iNO, high-frequency ventilation, and ECMO |
| Bialkowski et al. (2015) | Observational | Australia | Preterm and term neonates | Median 38.4 g.w.(range 35.5-39.3 g.w.) | Median 2.97 kg (range 2.69–3.57 k-g) | 18 | Hernia-PPHN | Echocardiographically confirmed (PAP and myocardial function) | Intravenous sildenafil (dose-adjust use) | intravenous | Five infants received iNO at 20 (range, 10–30 ppm) ppm before sildenafil |
| Herrera et al. (2006) | RCT | Mexico | Term neonates | / | Sildenafil group 2741 ± 660 g; control group 2651 ± 710 g | 24 | Idiopathic | Need for mechanical ventilation and OI > 51 | Oral sildenafil 2 mg/kg Q6h and ventilation | oral | No facility available to administer iNO |
| Limjoco et al. (2015) | Observational | America | Term and postterm neonates | 34 0/7–42 0/7 g.w. | Sildenafil group 3131 ± 512 g; control group 3234 ± 372 g | 17 | MAS, sepsis-PPHN | Echocardiographically confirmed (presence of right-to-left shunt or estimated PAP) mmHg) | Enteral "low-dose" (<3 mg/kg·d) and "high-dose" sildenafil (≥3 mg/kg·d) | enteral | Used iNO |

(Continues)

**TABLE 1** (Continued)

| Study | Design | Country | Patients | Age | Birth weight | Total number | PPHN Type | PPHN diagnosis | Intervention | Route | Use of iNO |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Sayed et al. (2015) | RCT | Egypt | Term neonates | 40.3 ± 1.0 g.w. | 3215 ± 348 g | 27 | Idiopathic | Echocardiographically confirmed (presence of right-to-left shunt or tricuspid regurgitation jet pressure >40 mmHg) | Oral sildenafil 1 mg/kg Q6h | oral | No facility available to administer iNO |
| Tan et al. (2015) | Observational | Australia | Pre-term neonates | 25.6 ± 1.3 g.w. | 631 ± 181 g | 42 | BPD-PPHN | Echocardiographically confirmed (estimate right ventricular systolic pressure by tricuspid regurgitation jet velocity (TRJVmax), RVSP = 4 TRJVmax^2- + 5, + 5 as the right atrial pressure) | Oral sildenafil (start at 0.25 mg/kg/dose Q8h, gradually increasing to a 1.5 mg/kg/dose over 2–3 weeks) | oral | One infant received iNO concomitantly |
| Vargas-Origel et al. (2010) | RCT | Mexico | Term and postterm neonates | ≥36 g.w. | Sildenafil group 2993 ± 532 g; control group 3043 ± 563 g | 51 | Idiopathic | Echocardiographically confirmed (presence of right-to-left shunt or estimated PAP) | Oral sildenafil or placebo (normal saline). ORAL Sildenafil: 3 mg/kg/dose Q6h. | oral | iNO was not available at the start of the trial, but it became available during the study |

Abbreivations: BPD, bronchopulmonary dysplasia; ECMO, extracorporeal membrane oxygenation; iNO, inhaled nitric oxide; MAS, meconium aspiration syndrome; PAP, pulmonary artery pressure; PPHN, persistent pulmonary hypertension of neonates; RCT, randomized controlled trials.

**TABLE 2** Summary of meta-analyses in randomized controlled trials

| Outcomes | Timepoints | No. of studies | $I^2$ | Model | SMD | 95% CI lower | 95% CI upper | Publication bias |
|---|---|---|---|---|---|---|---|---|
| Hemodynamic and pulmonary parameters | Mean airway pressure | | | | | | | |
| | At baseline | 2 | 0.0% | Fixed | −0.86 | −1.73 | −0.34 | / |
| | 1 h after treatment | 1 | / | Fixed | −1.03 | −1.89 | −0.17 | / |
| | 6 h after treatment | 2 | 67.2% | Fixed | −1.00 | −1.53 | −0.46 | / |
| | 24 h after treatment | 2 | 29.7% | Fixed | −1.87 | −2.50 | −1.23 | / |
| | 72 h after treatment | 1 | / | Fixed | −3.92 | −5.32 | −2.51 | / |
| | Mean pulmonary arterial blood pressure (mmHg) | | | | | | | |
| | At baseline | 2 | 83.7% | Fixed | 0.45 | −0.11 | 1.02 | / |
| | 6 h after treatment | 1 | / | Fixed | 3.93 | 1.96 | 5.90 | / |
| | 24 h after treatment | 1 | / | Fixed | −0.55 | −1.67 | 0.56 | / |
| | 36 h after treatment | 1 | / | Fixed | −0.77 | −1.91 | 0.37 | / |
| | 72 h after treatment | 2 | 76.2% | Fixed | 0.13 | −0.30 | 0.56 | / |
| | A-a$O_2$ difference | | | | | | | |
| | At baseline | 2 | 0.0% | Fixed | 0.02 | −0.47 | 0.52 | / |
| | 1 h after treatment | 1 | / | Fixed | −0.19 | −0.99 | 0.62 | / |
| | 6 h after treatment | 1 | / | Fixed | 0 | −0.80 | 0.80 | / |
| | 24 h after treatment | 2 | 67.4% | Fixed | −0.17 | −0.7 | 0.36 | / |
| | 72 h after treatment | 1 | / | Fixed | −1.76 | −2.72 | −0.81 | / |
| | $PaO_2$(mmHg) | | | | | | | |
| | At baseline | 2 | 29.1% | Fixed | 0.61 | 0.14 | 1.09 | / |
| | 1 h after treatment | 2 | 0.0% | Fixed | 0.52 | 0.05 | 0.99 | / |
| | 6 h after treatment | 2 | 0.0% | Fixed | 0.76 | 0.25 | 1.27 | / |
| | 24 h after treatment | 2 | 0.0% | Fixed | 0.86 | 0.31 | 1.41 | / |
| | 72 h after treatment | 1 | / | Fixed | 2.63 | 1.51 | 3.74 | / |
| | At the end of therapy | 1 | / | Fixed | 2.84 | 2.08 | 3.60 | / |
| Oxygenation indices | OI | | | | | | | |
| | At baseline | 2 | 0.0% | Fixed | −0.26 | −0.72 | 0.20 | / |
| | 1 h after treatment | 3 | 0.0% | Fixed | −0.67 | −1.11 | −0.24 | / |
| | 6 h after treatment | 2 | 57.7% | Fixed | −1.55 | −2.09 | −1.02 | / |
| | 24 h after treatment | 3 | 69.2% | Fixed | −1.51 | −2.07 | −0.95 | / |
| | 36 h after treatment | 1 | / | Fixed | −3.15 | −5.40 | −0.89 | / |
| | 72 h after treatment | 1 | / | Fixed | −4.02 | −5.45 | −2.59 | / |
| | At the end of therapy | 1 | / | Fixed | −3.06 | −3.85 | −2.27 | / |
| | Mean change of OI | | | | | | | |
| | 1 h after treatment | 1 | / | Fixed | −1.68 | −2.97 | −0.38 | / |
| | 24 h after treatment | 1 | / | Fixed | −2.54 | −4.14 | −0.94 | / |
| | 30 h after treatment | 1 | / | Fixed | −6.63 | −9.93 | −3.33 | / |
| | 36 h after treatment | 1 | / | Fixed | −2.98 | −5.16 | −0.80 | / |

(Continues)

**TABLE 2** (Continued)

| Outcomes | Timepoints | No. of studies | $I^2$ | Model | SMD | 95% CI lower | 95% CI upper | Publication bias |
|---|---|---|---|---|---|---|---|---|
| Duration | Duration of hospital stay (days) | 1 | / | Fixed | 0.40 | −0.42 | 1.21 | / |
| | Duration of mechanical ventilation (days) | 1 | / | Fixed | 0.38 | −0.43 | 1.20 | / |
| | Days of intubation (days) | 1 | / | Fixed | −1.19 | −2.07 | −0.31 | / |

| Outcomes | No. of studies | $I^2$ | Model | RR | 95% CI lower | 95% CI upper | Publication bias |
|---|---|---|---|---|---|---|---|
| Mortality | 4 | 34.9% | Fixed | 0.27 | 0.12 | 0.61 | Begg: 1.000<br>Egger: 0.653 |
| Other adverse outcomes | 4 | 20.6% | Fixed | 0.54 | 0.36 | 0.8 | Begg: 0.100<br>Egger: 0.061 |

Abbreviation: CI, confidence interval; OI, oxygenation index.

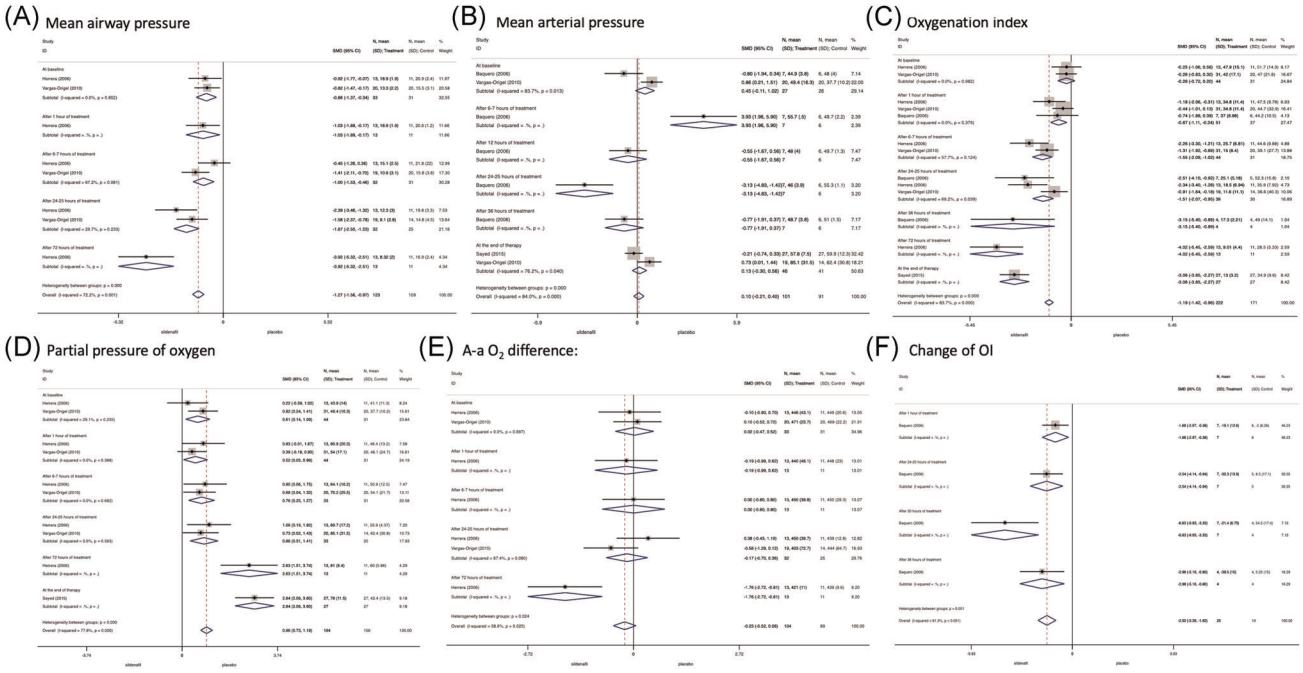


**FIGURE 2** Hemodynamic, pulmonary and oxygenation parameters in randomized clinical trials. (A) Mean airway pressure; (B) mean arterial pressure; (C) oxygenation index; (D) partial pressure of oxygen; (E) A-a $O_2$ difference; (F) Change of oxygenation index

significantly decreased the A-a $O_2$ difference 72 h posttreatment (*SD*: −1.76, 95% CI: −2.72, −0.81), favoring the sildenafil treatment.

### 3.2.5 | Oxygenation parameters

*Oxygenation index (OI)*

With placebo as the control, a total of three RCT studies were included for the evaluation of OI, as shown in Table 2. At baseline, there were no significant differences between the use of sildenafil and control (SMD: −0.26, 95% CI: −0.72, 0.20; $I^2 = 0.0\%$ at baseline), and the 95% CI crossed the null hypothesis. After the first dose, OI significantly decreased in sildenafil group (SMD: −0.67, 95% CI: −1.11, −0.24; $I^2 = 0.0\%$ after the first dose). A time-dependent pattern of OI elevation after the intervention of sildenafil can be obviously discerned. After 24 h of treatment, difference between the two groups widened, where the use of sildenafil greatly decreased the OI (*SD*: −1.51, 95% CI: −2.07, −0.95; $I^2 = 69.2\%$) despite the high heterogeneity. Sildenafil exerted the effects to the greatest level after 72 h of treatment (*SD*: −4.02, 95% CI: −5.45, −2.59; $I^2$ = inapplicable).

Only one RCT study[38] reported the mean changes of OI with regard to the baseline, as shown in Table 2. A time-dependent pattern of improvement was also observed, and overall, sildenafil greatly lowered the mean change of OI (*SD*: −2.98, 95% CI: −5.16, −0.80; $I^2$ = inapplicable).

*$FiO_2$*

Only one nonrandomized observational study reported the $FiO_2$, as shown in Table 3. However, sildenafil was not favored after 72 h of treatment because the combined effects crossed the null hypothesis (*SD*: 0.35, 95% CI: −0.58, 1.28; $I^2$ = inapplicable).

### 3.2.6 | Adverse outcomes

*Mortality*

A total of four RCT studies reported data on sildenafil mortality as shown in Table 2 and Figure 3, showing a great reduction in mortality

**TABLE 3** Summary of meta-analyses in non-randomized observational studies

| Outcomes | Timepoints | No. of studies | $I^2$ | Model | SMD | 95% CI lower | 95% CI upper | Publication bias |
|---|---|---|---|---|---|---|---|---|
| Hemodynamic parameters | Mean pulmonary arterial blood pressure (mmHg) | | | | | | | |
| | At baseline | 1 | / | Fixed | −0.21 | −1.17 | 0.76 | / |
| | 6 h after treatment | 1 | / | Fixed | −0.87 | −1.89 | 0.14 | / |
| | 12 h after treatment | 1 | / | Fixed | −1.62 | −2.74 | −0.49 | / |
| | 24 h after treatment | 1 | / | Fixed | −1.05 | −2.08 | −0.01 | / |
| | 36 h after treatment | 1 | / | Fixed | −1.44 | −2.54 | −0.35 | / |
| | 72 h after treatment | 1 | / | Fixed | −0.5 | −1.48 | 0.49 | / |
| Oxygenation indices | OI | | | | | | | |
| | 24 h after treatment | 1 | / | Fixed | 0.05 | −0.87 | 0.98 | / |
| | 72 h after treatment | 1 | / | Fixed | 0.72 | −0.23 | 1.68 | / |
| | $FiO_2$ | | | | | | | |
| | 24 h after treatment | 1 | / | Fixed | −0.18 | −1.1 | 0.75 | / |
| | 72 h after treatment | 1 | / | Fixed | 0.35 | −0.58 | 1.28 | / |
| Echocardiography parameters | RV TDI myocardial velocities (systolic) | | | | | | | |
| | 24 h after treatment | 1 | / | Fixed | −0.22 | −1.14 | 0.71 | / |
| | 72 h after treatment | 1 | / | Fixed | −0.24 | −1.17 | 0.69 | / |
| | RV TDI myocardial velocities (diastolic) | | | | | | | |
| | 24 h after treatment | 1 | / | Fixed | 0.03 | −0.9 | 0.95 | / |
| | 72 h after treatment | 1 | / | Fixed | 0.23 | −0.7 | 1.15 | / |
| | RVSP (mmHg) | | | | | | | |
| | 24 h after treatment | 1 | / | Fixed | 0.81 | −0.16 | 1.77 | / |
| | 72 h after treatment | 1 | / | Fixed | 0.92 | −0.06 | 1.89 | / |
| | RVO (ml/kg/min) | | | | | | | |
| | 24 h after treatment | 1 | / | Fixed | −0.34 | −1.27 | 0.59 | / |
| | 72 h after treatment | 1 | / | Fixed | −0.77 | −1.73 | 0.19 | / |

| Outcomes | No. of studies | I-square | Model | RR | 95% CI lower | 95% CI upper | Publication bias |
|---|---|---|---|---|---|---|---|
| Mechanical ventilation | 3 | 0.0% | Fixed | 1.2 | 0.75 | 1.92 | / |
| Oxygen requirement at discharge | 1 | / | Fixed | 1.43 | 0.66 | 3.11 | / |
| Mortality | 5 | 22.3% | Fixed | 0.3 | 0.14 | 0.64 | Begg: 1.000<br>Egger: 0.649 |

Abbreviations: RVSP, right ventricular systolic pressure; RVO, right ventricular outflow.

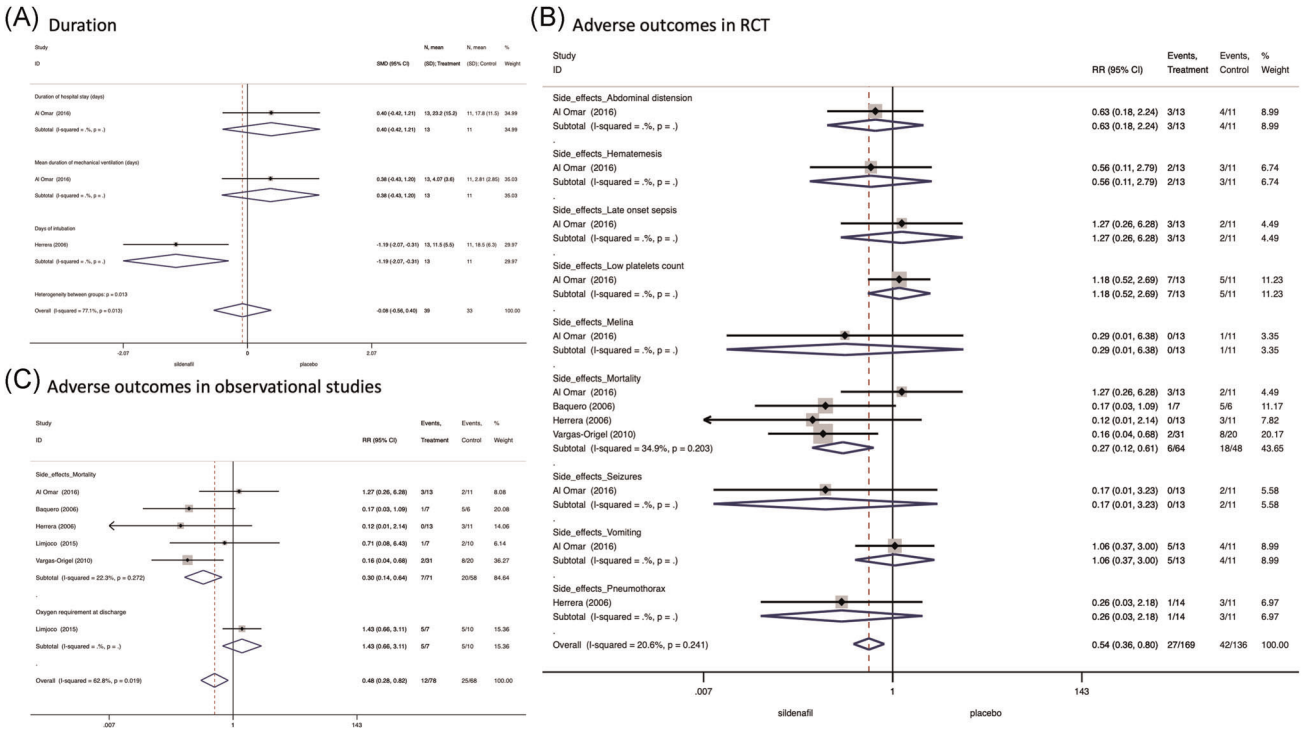


**FIGURE 3** Adverse outcomes secondary to the use of sildenafil versus placebo in randomized clinical trials. (A) duration of hospital stay, mechanical ventilation and intubation; (B) adverse outcomes in randomized clinical trials; (C) adverse outcomes in observational studies [Color figure can be viewed at wileyonlinelibrary.com]

rate for the sildenafil group versus the placebo group (RR: 0.27, 95% CI: 0.12, 0.61; $I^2$ = 34.9).

As for nonrandomized studies, five studies reported data concerning mortality, and the results also showed low mortality in PPHN neonates taking sildenafil (RR: 0.30, 95% CI: 0.14, 0.64; $I^2$ = 22.3%), as shown in Table 3.

### *Safety of sildenafil*

A total of four RCT reported the occurrences of adverse outcomes in sildenafil use, including abdominal distension, hematemesis, late-onset sepsis, low platelets count, melena, seizures, vomiting, and pneumothorax, as well as the duration of hospital stay. All the occurrences of adverse outcomes were decreased in children using sildenafil (RR: 0.54, 95% CI: 0.36, 0.80, $I^2$ = 20.6%).

Regarding the nonrandomized observational study, increased use of mechanical ventilation were observed in neonates taking sildenafil (RR: 1.2, 95% CI: 0.75, 1.92, $I^2$ = 0.0%), as shown in Table 3. As for duration, only one RCT reported the length of hospital stay (days, SMD: 0.40, 95% CI: −0.42, 1.21, $I^2$ = not applicable), and the duration of mechanical ventilation. Herrera et al. reported the days of intubation, which showed obvious reduction with the use of sildenafil (RR: −1.19, 95% CI: −2.07, −0.31, $I^2$ = inapplicable).

### *Other outcomes*

Moreover, the outcomes of echocardiography and cardiac catheterization parameters were reported, as shown in Table 3, including systolic and diastolic right ventricular tissue Doppler imaging (TDI) myocardial velocities, right ventricular systolic pressure (RVSP) (mmHg), and right ventricular outflow (RVO) (ml/kg/min). Only one observational cohort study reported such outcomes, and no obvious differences between the sildenafil and the control group were found in all these outcomes, and all their 95% CI crossed the null hypothesis.

### *Publication bias*

To assess the risk of bias, we performed Begg's and Egger's test of the major outcomes and found that the publication biases were not significant (Table 2). Subgroup analyses by timepoints were performed in each outcome, as shown in Table 2.

## 4 | DISCUSSION

This meta-analysis provides evidence on sildenafil use for PPHN treatment in term and premature neonates. Generally, improvements were seen in hemodynamic metrics (PAP, and mean arterial blood pressure), oxygenation (A-a $O_2$ difference, $PaO_2$, oxygenation index, $FiO_2$), cardiac catheterization measurements (pulmonary vascular resistance), adverse outcomes (all-cause mortality), and a series of echocardiographic parameters (Table 2). This is concordant with findings of an earlier meta-analysis.[30] Moreover, the assessment of hemodynamic parameters by echocardiography demonstrated improvement with sildenafil across the heterogeneous population, including PPHN and congenital diaphragmatic hernia as well as BPD,

indicating that these subgroups of PPHN may also benefit from sildenafil use.

PPHN has been defined as PH with a failed postnatal decrease in pulmonary vascular resistance (PVR), PH associated with CDH/lung hypoplasia, and PH in BPD/neonatal chronic lung disease.[11] Sildenafil use is associated with increased $PaO_2$ and decreased OI and alveolar-arterial gradient in the five RCT studies included for the evaluation of oxygenation index as shown in Table 2.[36–40] We found that there was certain evidence that sildenafil use improved oxygenation parameters and clinical outcomes, with fewer adverse events when compared with either baseline measurements or the use of placebo (Figure 2). Besides, a significant reduction in pulmonary pressures was noted. Moreover, the use of sildenafil has been shown to improve physiologic/hemodynamic assessments, significantly improving the echocardiographic markers of PAH and reduced $FiO_2$ (Table 2), but their clinical significance in predicting the prognosis remains uncertain.[41]

The most commonly reported adverse events at the recommended 20 mg tid oral dose among patients receiving sildenafil therapy included retinopathy, epistaxis, headache, dyspepsia, and flushing; their prevalence is around 6% or higher.[42] The START-2 trial, reported in the study by Barst et al. that increased 2-year mortality was noted in children aged 1–17 years after receiving high-dose sildenafil.[43]

Therefore, toxicities were a major focus in this review. Nevertheless, in our review, only late-onset sepsis was found positively related to sildenafil use.[44] Sildenafil is unlikely at fault for the majority of side effects, and mortality may be attributable to the underlying pulmonary vascular disease instead of sildenafil use.

Moreover, in the pooled meta-analysis, only one cohort study reported data on mortality, and sildenafil use is highly associated with neonatal deaths (RR: 39.00, 95% CI: 5.39, 282.03, $I^2$ = inapplicable, Figure 7B)[44]; however, the RCT pooled showed a reduction in mortality, except for Barst et al., being the only RCT that reported increased mortality associated with sildenafil use (RR: 0.7, 95% CI: 0.3, 1.66, $I^2$ = 59.2%).[43,44] Nevertheless, the lower bound of the 95% confidence interval was 0.3, showing that clinically important benefits fell outside the confidence interval, meaning the possibility of the sildenafil use increasing mortality could not be ruled out. Moreover, most patients were critically ill, and sildenafil was thought as the last resort, thus mortality rates were extremely high in cohort study.[44] Still, large multicenter trials have reported that, like its counterpart, iNO, Sildenafil also did not reduce mortality or the need for ECMO.[41] Therefore, clinical trials on neonates with

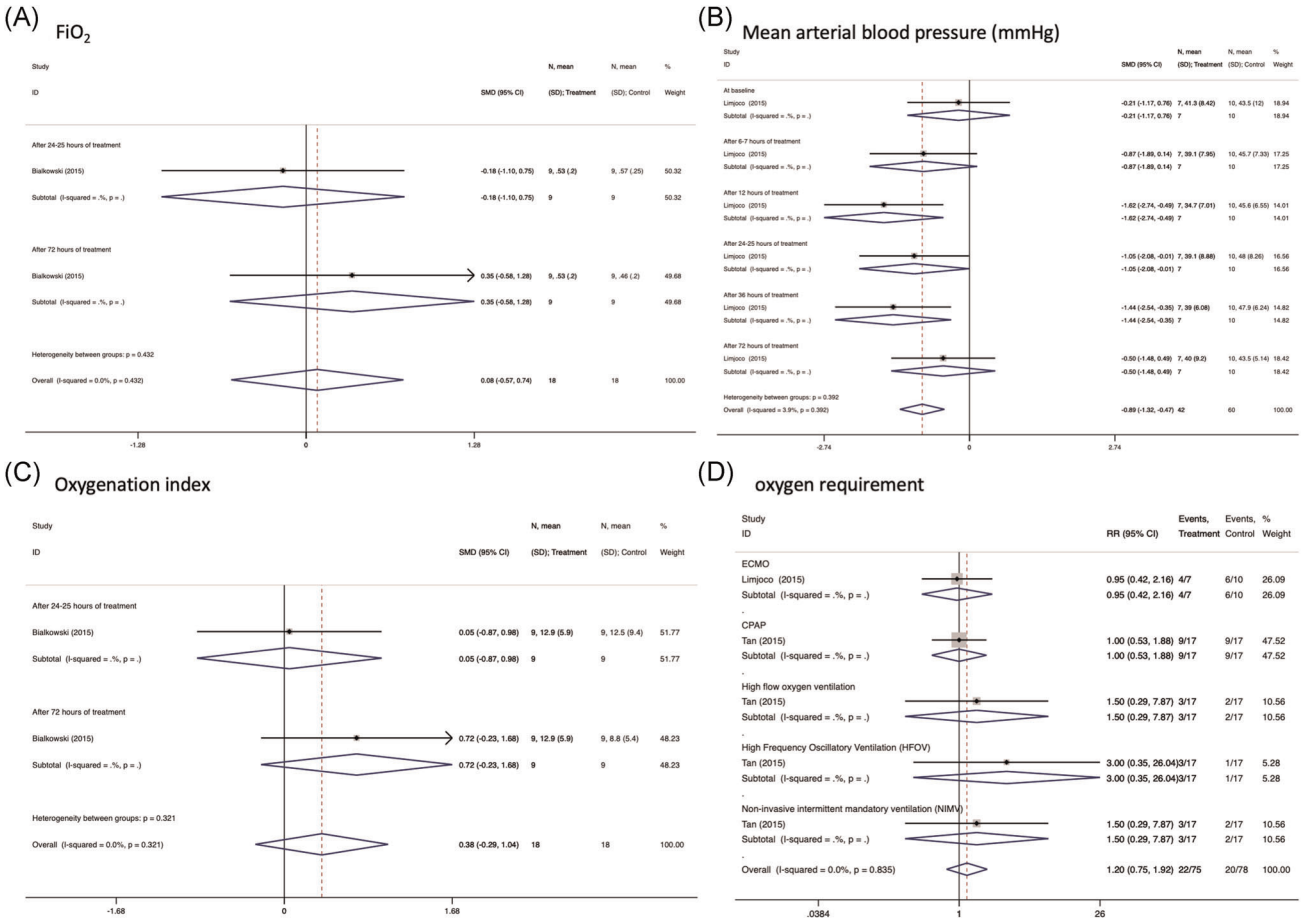


**FIGURE 4** Hemodynamic, pulmonary and oxygenation parameters in observational studies. (A) Fraction of inspired oxygen; (B) mean arterial pressure; (C) oxygenation index; (D) oxygen requirement [Color figure can be viewed at wileyonlinelibrary.com]

similar conditions of PPHN are needed to confirm the side effects of the use of sildenafil more rigorously.

Although we performed subgroup analysis and sensitivity analysis by stepwise subtracting each article, heterogeneity still exists, which may be attributable to the controversy over the timing of initiation and the dosage of sildenafil use. Moreover, in some studies, sildenafil was used right after the cessation of other therapy like iNO, Milrinone, bosentan, or calcium channel blockers,[45] rendering it controversial if the echocardiographic improvements were credited to the sildenafil use. Previous investigations by Shekerdemian et al. in a piglet model of meconium aspiration suggested that the use of iNO and sildenafil together resulted in hypotension and worsened oxygenation.[46] Therefore, insights on potentially future larger-scale RCT trials could define the use of sildenafil as a second agent and as adjuvant therapy for decreasing the need for ECMO and mortality. Multicenter research is needed to further evaluate the dose–response relationships and long-term effects of sildenafil use in neonates.

There are limitations of this study that need addressing. First, though the present study has systematically searched articles published in certain major databases, the conference abstracts or unpublished articles that may contain eligible data were not searched. Nevertheless, we analyzed all types of studies available regarding the use of sildenafil, including RCT and nonrandomized observational studies to comprehensively review the use of sildenafil, and with the data analyzed separately, the heterogeneity between different study types was minimized. Second, only English articles and one Spanish article were included, thus relevant studies published in other languages may have been missed. Third, owing to a small number of studies included, subgroup analysis and sensitivity analysis was not possible to trace the origins of heterogeneity. Fourth, owing to the limited number of studies included and the small number and mixed characteristics of neonates pooled, premature and term neonates as well as postterm infants were not distinguished in the study, and the conclusion of the present study should be interpreted with caution (Figure 4).

Therefore, there remains the need for creative trial designs to overcome the difficulties of studying rare and heterogeneous patient population and for long-term continuation of blinded dose-ranging for adverse event surveillance.[47] More robust pediatric pharmacokinetic and safety data are also required.

## 5 | CONCLUSION

This systematic review showed improved hemodynamic and oxygenating parameters as well as safety profiles of sildenafil in treating neonates with PPHN. But owing to the high heterogeneity and limited information, the positive results should be interpreted cautiously, and future studies with robust longitudinal or randomized controlled design, especially on long-term effects of the use of sildenafil are needed to further evaluate the utility, efficacy, dosage, timing, and safety of sildenafil use.

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## CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

## AUTHOR CONTRIBUTIONS

**Zonglin He**: Conceptualization (equal); data curation (equal); formal analysis (equal); methodology (equal); visualization (equal); writing original draft (lead); writing review and editing (equal). **Sui Zhu**: Conceptualization (equal); project administration (equal); writing original draft (equal); writing review and editing (equal). **Kai Zhou**: Conceptualization (equal); data curation (equal); formal analysis (equal); writing original draft (supporting); writing review and editing (equal). **Ya Jin**: Project administration (equal); resources (equal); software (equal); writing original draft (supporting); writing review and editing (supporting). **Longkai He**: Project administration (equal); resources (equal); writing original draft (supporting); writing review and editing (supporting). **Weipeng Xu**: Validation (equal); writing original draft (supporting); writing review and editing (supporting). **CheokUn Lao**: Investigation (equal); writing original draft (supporting); writing review and editing (supporting). **Liu Guosheng**: funding acquisition (equal); visualization (equal); writing original draft (supporting); writing review and editing (supporting). **Shasha Han**: funding acquisition (equal); project administration (equal); writing original draft (equal); writing review and editing (equal).

## DATA AVAILABILITY STATEMENT

Data available on reasonable request from the authors.

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## SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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