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Effect of NO inhalation on ECMO use rate and mortality in infants born at or near term with respiratory failure

Xiaoqing Wang, MD*, Bowen Li, MD, Yuqing Ma, MD, Hong Zhang, MD

Abstract

Background: The molecular studies showed that Nitric oxide (NO) is an essential factor which regulates pulmonary artery tension. However, the conclusions of existing clinical studies were inconsistent.

Objective: This meta-analysis is aimed to determine whether the inhalation of NO could improve oxygenation and reduce rate of death and use of extracorporeal membrane oxygenation (ECMO).

Methods: The strategies used to search PubMed, The Cochrane Central Register of Controlled trials in the Cochrane Library, Embase, Web of science, Clinical Trials Registry, and China Biology Medicine disc, from inception to February, 2018. The primary outcomes were death or use of ECMO, death before hospital discharge, use of ECMO before hospital discharge, change in PaO2 after treatment. We assess the risk of bias in each included study by Cochrane Handbook, and calculated typical estimates of RR, each with its 95% CI, and for continuous outcomes, WMD or a summary estimate for SMD, each with its 95% CI.

Results: Nine randomized controlled trials (RCTs) with a total of 856 participants were included in this meta-analysis. This meta-analysis revealed that the experimental group had significantly lower death or use of ECMO (RR 0.66, 95% CI 0.57–0.77, $I^2=0\%$, $P<.00001$) and lower use of ECMO before hospital discharge (RR 0.89, 95% CI 0.50–0.71, $I^2=0\%$, $P<.00001$) compared to control group. And in the infants without diaphragmatic hernia, experimental group had significantly higher change in PaO2 after treatment (MD 50.40, 95% CI 32.14–68.66, $P<.00001$). The meta-analysis also showing a tendency to improve in the death before hospital discharge (RR 0.89, 95% CI 0.60–1.31, $I^2=0\%$, $P=.55$) and the change in PaO2 after treatment of the infants with diaphragmatic hernia (MD 6.70, 95% CI −2.32 to 15.72, $P<.00001$, $P=.15$), but no difference between experimental group and control group.

Conclusion: We found that NO inhalation can improve oxygenation and reduce rate of death and use of ECMO in this meta-analysis. Therefore, we recommend the use of NO inhalation for infants born at or near term with respiratory failure.

Abbreviations: A-aDO2 = alveoliarterial oxygen difference, ECMO = extracorporeal membrane oxygenation, NO = nitric oxide, PaO2 = partial pressure of oxygenin arterial blood, PPHN = Persistent pulmonary hypertension of the newborn, ppm = parts per million, RCTs = randomized controlled trials.

Keywords: ECMO, hypoxemia, meta-analysis, newborn, nitric oxide

1. Introduction

Severe hypoxemia caused by neonatal respiratory failure is the most common cause of neonatal death.[1] Hypoxemia is an indication of extracorporeal membrane oxygenation (ECMO, a technique of providing both cardiac and respiratory support with an artificial lung). Moreover, traditional therapies (such as mechanical ventilation neuromuscular blockade, and sedation) contributed little to reducing mortality and the need of ECMO. However, ECMO is an invasive therapy which can lead to the incidence of hemorrhagic complications.[2] Therefore, an effective therapy with fewer side effects is widely needed.

Nitric oxide (NO), a vital factor which regulates vascular muscle tone at the cellular level occurs.[3] It is approved that NO could regulate pulmonary artery tension to relieve pulmonary hypertension. A study[4] indicated that the inhibition of NO formation induced sheep fetal pulmonary and systemic hypertension with reduction of the rise in pulmonary blood flow during delivery. Similar study[5] showed that ovine fetus inhaled NO induced selective and sustained pulmonary vasodilation. In addition, several studies[6–8] showed that the inhalation of 40 to 80 parts per million (ppm) of NO change pulmonary vasoconstriction on the premise of no effect on the systemic circulation. The clinical studies[9] of newborns with severe sustained pulmonary hypertension indicated that inhaled NO rapidly enhanced preductal oxygen saturation, and side effects were non-detectable.

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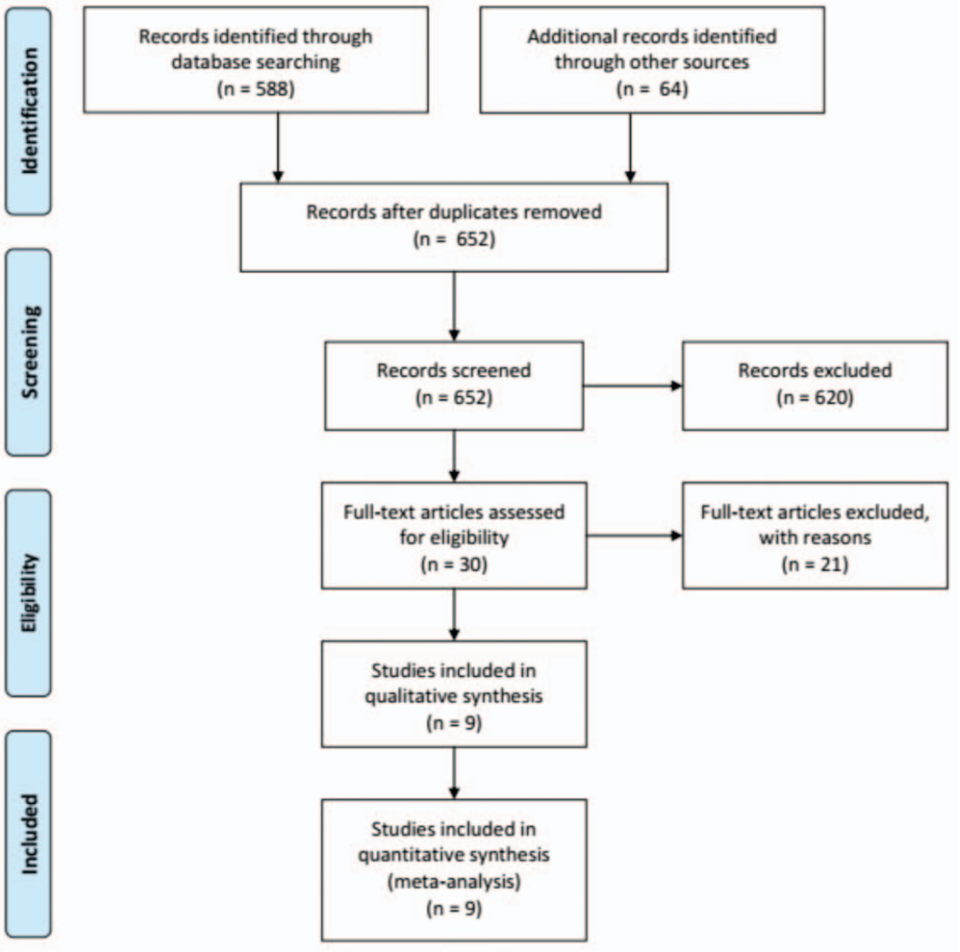

Figure 1. Flow chart of the meta-analysis selection process for eligible studies.

Thus, NO may has an effect on hypoxemia by regulating vascular muscle tone. Several clinical studies have been conducted; however, the conclusions were inconsonant.[9–11] Therefore, this meta-analysis is aimed to determine whether the inhalation of NO could improve oxygenation and reduce rate of death and use of ECMO.

2. Materials and methods

2.1. Search strategy

The strategies used to search PubMed, The Cochrane Central Register of Controlled trials in the Cochrane Library, Embase, Web of science, Clinical Trials Registry and China Biology Medicine disc, from inception to June, 2018. The following search terms were used: Nitric, NO, neonates, newborn, respiratory failure. The reference lists of all identified relevant articles were assessed to identify further pertinent studies. We applied no language restrictions.

2.2. Inclusion and exclusion criteria

Studies were included if they were RCT. The participants of this study were newborn infants (<1 month of age) with hypoxemia suspected to be due to lung disease, pulmonary hypertension with right-to-left shunting or both. The infants (>34 weeks' gestation) were included. Studies compared administration of iNO gas versus control—no gas or placebo gas. The primary outcomes were the rate of death or use of ECMO, death before hospital discharge, use of ECMO before hospital discharge. The secondary outcomes were the change in PaO2 after treatment.

Studies were excluded

1. infants with intracardiac shunting due to structural congenital heart disease;
2. infants (<1 month of age) with hypoxemia due not to lung disease;
3. the gestation was <34 weeks;
4. articles with insufficient data and published repeatedly;
5. review articles and case report.

2.3. Study selection and data extraction

Two reviewers independently screened titles and abstracts of search results. If a title and abstract could not be rejected with certainty by both reviewers, the full text of the paper was retrieved and assessed for eligibility. Any disagreement among reviewers was resolved by discussion and consensus or, if needed, divergence in opinion with respect to inclusion criteria was evaluated by the third investigator.

Table 1

Characteristics of nine included studies of this meta-analysis.

Study (year)	Number of participant (cases/controls)	Gestational age	Oxygenation	Intervention	Control	Outcomes
Christou et al (2000)	21/20	≥34 weeks	$PaO_2 < 100$ mmHg	40 ppm iNO reduced to 20 ppm after 1 hour.	No gas	1, 2, and 3
Clark et al (2000)	113/104	≥34 weeks	OI ≥ 25	20 ppm iNO	Nitrogen placebo	1, 2, and 3
Davidson et al (1997)	114/41	≥34 weeks	PaO2 between 40 and 100 mmHg	Inhaled nitric oxide at 5, 20 or 80 ppm	Nitrogen placebo	1, 2, and 3
Innovo et al (2007)	29/31	≥34 weeks	Not mentioned	iNO at 20 ppm	No gas	1, 2, and 3
Liu et al (2008)	21/25	≥36 weeks	OI > 25	iNO at 15 ppm	No gas	1 and 2
Ninos et al (1996)	114/121	≥34 weeks	OI ≥ 25	iNO at 20 ppm	No gas	1, 2, 3, and 4
Ninos et al (1997)	21/23	≥34 weeks	Not mentioned	iNO at 20 ppm	No gas	4
Roberts et al (1996)	30/28	≥37 weeks	PaO2 < 55 mmHg	iNO at 80 ppm	No gas	1, 2, and 3

Two reviewers independently extracted following data from all eligible articles: basic information; study characteristics (gestational age, the number of participants, oxygenation); outcomes (the rate of death or use of ECMO, death before hospital discharge, use of ECMO before hospital discharge, the change in PaO2 after treatment). Any disagreement was resolved by discussion and consensus or, if needed, third party arbitration.

2.4. Quality assessment

We assess the risk of bias in each included study by Cochrane Handbook.[1] The assessment criteria were random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting and other type of bias.

2.5. Statistical analysis

We performed meta-analysis by using RevMan version 5.3, as supplied by Cochrane. We calculated typical estimates of RR, each with its 95% CI, and for continuous outcomes, WMD or a summary estimate for SMD, each with its 95% CI. Statistical heterogeneity was examined by calculating the I^2 statistic. We used random-effects model when $I^2 > 50\%$; otherwise, a fixed-effects model was considered when $I^2 < 50\%$.

2.6. Ethics and dissemination

Ethical approval is not required in this meta-analysis, because it is based on a second study of some previously published data.

3. Results

3.1. Result of search

There were 652 relevant articles identified, 641 studies of which were exclude. Figure 1 details the number of studies identified at each stage of the searching process. There were 9 studies met our selection criteria.[7,9–16]

3.2. Description and quality of the included studies

Nine RCTs were included in this meta-analysis. A total of 856 participants were included in this meta-analysis, 463 were assigned into the experimental group and 393 to the control group. Table 1 details the Characteristics of nine included studies of this meta-analysis. The risk of bias of all studies are detailed in Table 2.

3.3. Effects of interventions

3.3.1. Death or use of ECMO. Death or use of ECMO of 373 participants were reported in eight studies.[9–16] In this meta-analysis, we found that the experimental group had significantly lower death or use of ECMO than the control group (RR 0.66, 95% CI 0.57–0.77, $I^2 = 0\%$, $P < .00001$) (Fig. 2).

3.4. Death before hospital discharge

Eight studies[9–16] reported the death before hospital discharge in 92. Meta-analysis revealed the experimental group had a tendency to reduce the death before hospital discharge compared

Table 2

Risk of bias in the included studies.

Study (year)	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Christou et al (2000)	Unclear risk	Low risk	high risk	Low risk	Unclear risk
Clark et al (2000)	Low risk	Low risk	Low risk	Low risk	Unclear risk
Davidson et al (1997)	Unclear risk	Low risk	Low risk	Low risk	Unclear risk
Innovo et al (2007)	Low risk	Low risk	high risk	Low risk	Low risk
Liu et al (2008)	Unclear risk	Unclear risk	high risk	Low risk	Unclear risk
Ninos et al (1996)	Low risk	Low risk	Low risk	Low risk	Low risk
Ninos et al (1997)	Low risk	Low risk	Low risk	Low risk	Unclear risk
Roberts et al (1996)	Unclear risk	Low risk	Low risk	Low risk	Unclear risk
Wessel et al (1996)	Unclear risk	Unclear risk	high risk	Low risk	Unclear risk

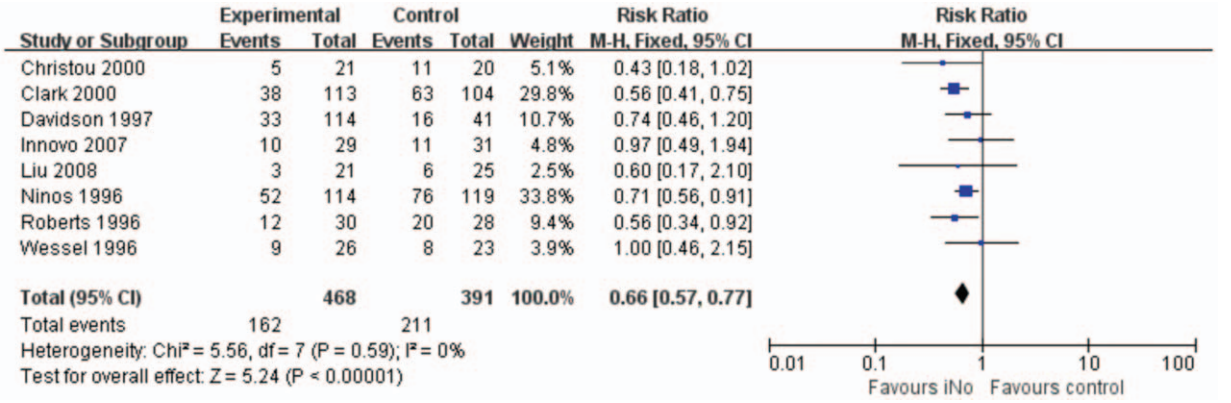

Figure 2. Forest plot of the rates of death or use of ECMO in participants treated with the inhalation of NO.

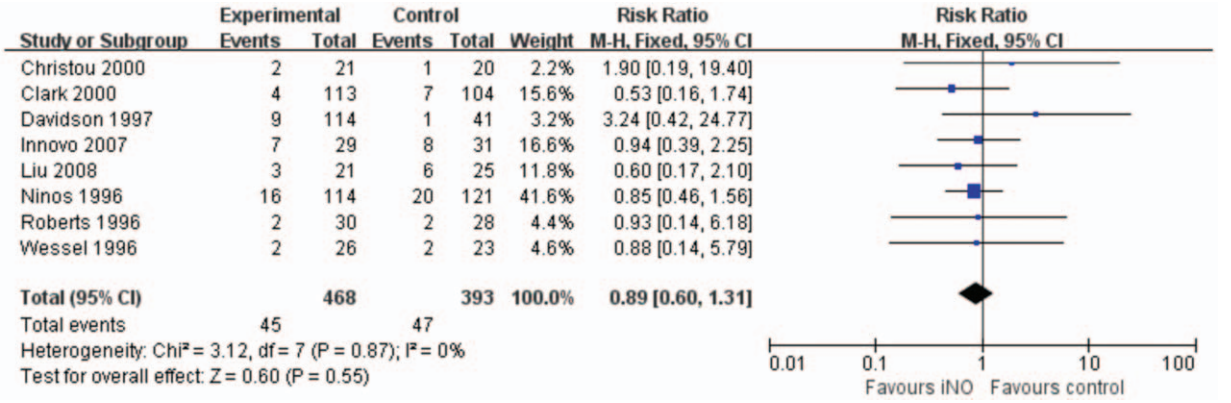

Figure 3. Forest plot of the rates of death before hospital discharge in participants treated with the inhalation of NO.

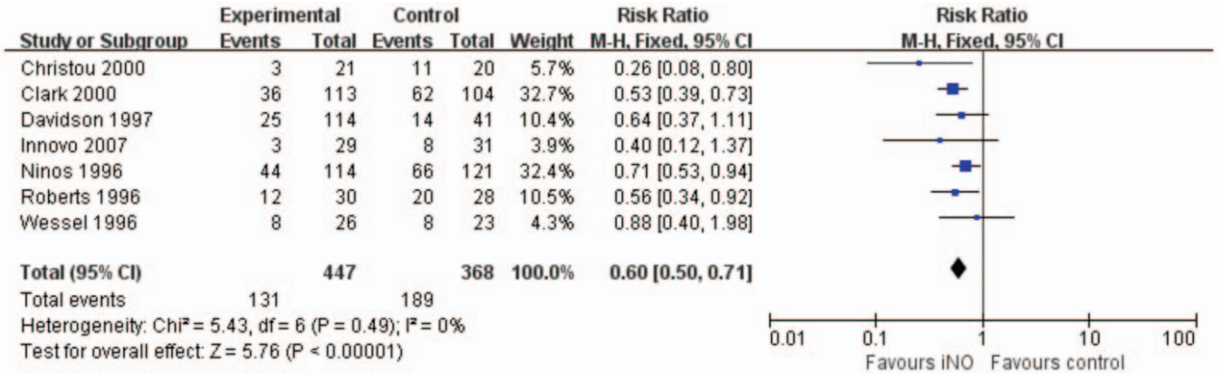

Figure 4. Forest plot of the rates of use of ECMO before hospital discharge in participants treated with the inhalation of NO.

to control group, but there was no significant difference between experimental group and control group (RR 0.89, 95% CI 0.60 to 1.31, $I^2 = 0\%$, $P = .55$) (Fig. 3).

3.5. Use of ECMO before hospital discharge

Seven studies[8–13,15] reported the use of ECMO before hospital discharge in 92 participants. This meta-analysis revealed that the experimental group had significantly lower use of ECMO before hospital discharge compared to control group (RR 0.89, 95% CI 0.50–0.71, $I^2 = 0\%$, $P < .00001$) (Fig. 4).

3.6. Change in PaO2 after treatment

There were only two studies[9,12] reported change in PaO2 after treatment in 277 participants (Fig. 4). The subgroup analysis

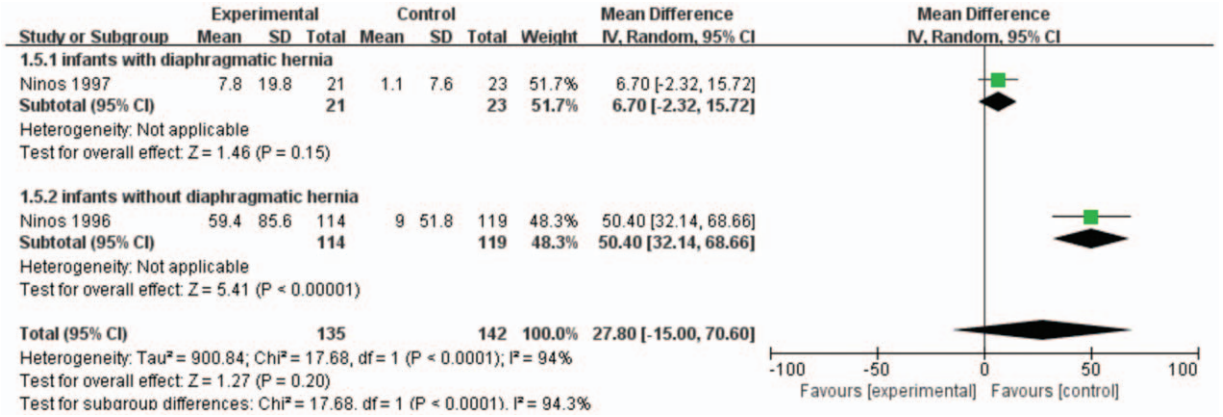

Figure 5. Forest plot of the Change in PaO2 after treatment in participants treated with the inhalation of NO.

revealed that the experimental group had significantly higher change in PaO2 after treatment (MD 50.40, 95% CI 32.14–68.66, $P < .00001$) compared to control group in the infants without diaphragmatic hernia. In the infants with diaphragmatic hernia, we found that the experimental group had a tendency to increase the change in PaO2 after treatment compared to control group, but there was no significant difference between experimental group and control group. (MD 6.70, 95% CI −2.32 to 15.72, $P < .00001$, $P = .15$) (Fig. 5).

4. Discussion

We included newborn infants (gestational age ≥34 weeks) with hypoxemia to determine the effect on oxygenation and the rate of death and use of ECMO. Our meta-analysis indicated that newborns with respiratory failure who inhaled NO had significantly less rate of death or use of ECMO and use of ECMO before hospital discharge, the less rate of death before hospital discharge was founded in the experimental group, and the PaO2 (partial pressure of oxygenin arterial blood) was improved, but statistical significance. In addition, the subgroup analysis stratified by whether infants had diaphragmatic hernia indicated that the inhalation of NO had better improvement effect on infants without diaphragmatic hernia compared infants with diaphragmatic hernia. Therefore, the inhalation of NO had a well therapeutic effect on newborn infants with hypoxemia.

Persistent pulmonary hypertension of the newborn (PPHN) plays a momentous role in the incidence of cardiorespiratory failure in the newborn infants. The primary persistent pulmonary hypertension, respiratory distress syndrome, aspiration of meconium, pneumonia or sepsis, and congenital diaphragmatic hernia are the commonest etiological factor of PPHN.[14,16] The traditional therapies of PPHN included paralysis, sedation, and used hyperventilation or base infusion to induce alkalosis, and used magnesium sulfate and adenosine to implement the diastole of pulmonary vessels.[17–20] However, these therapies did not improve the condition of cardiorespiratory failure for the most part. Moreover, significant heterogeneity and diversity of these therapies in application were founded by Walsh-Sukys.[19] ECMO was used to providing both cardiac and respiratory support with an artificial lung to treat PPHN. However, ECMO is an invasive therapy, and it is relevant with obvious neurodevelopmental deficits. NO is a vital regulatory factor for pulmonary vascular tension. The inhalation of NO plays an important role in improve mismatching ventilation/perfusion. Moreover, a clinical study indicated that the inhalation of NO could significantly improve PaO2 and reduce A-aDO2 (alveoliarterial oxygen difference). However, it is doubtful whether using NO to treat PPHN have risk of toxicity.[21] It has been proven that inhaled high doses of NO (80 ppm) in a neonatal ventilator can produce 5 ppm NO_2 in less than 20 s. Therefore, we need to use applicable dose of NO and detect the relevant index of NO (such as methaemoglobin leve).

However, limitations were ineluctable in the current meta-analysis. There only two studies which reported change in PaO2 after treatment, the strength of this outcome may be affected. The significant heterogeneity was founded in the index of the Change in PaO2 after treatment, and thus, the subgroup analysis was executed. There are two different interventions in control group (no gas and nitrogen placebo). Moreover, different doses of inhalational NO (15–80 ppm) may affect therapeutic effect. The impacts of different interventions in control group and doses of inhalational NO may be caused clinical heterogeneity. Therefore, larger, geographically dispersed multicenter RCTs should be performed to acquire the most precise conclusions.

5. Conclusion

The meta-analysis included 9 RCTs with 856 participants to investigate the effect of NO inhalation on oxygenation and the rate of death and use of ECMO. Better clinical outcomes of newborn infants with respiratory failure were found in patients treated with NO inhalation. The present meta-analysis suggests that the inhalation of NO is a superior therapy. Therefore, we recommend newborn infants should receive the therapy of NO inhalation. However, further well-designed multicenter RCTs with larger sample size are warranted to confirm our findings.

Author contributions

WXQ planed and designed the research; LBW and MYQ tested the feasibility of the study; WXQ and ZH wrote the manuscript; all authors approved the final version of the manuscript.
Data curation: Wang xiaoqing, Bowen Li.
Formal analysis: Wang xiaoqing.
Investigation: Wang xiaoqing.
Methodology: Wang xiaoqing, Yuqing Ma.
Resources: Hong Zhang.

Software: Wang xiaoqing, Hong Zhang.
Writing – original draft: Wang xiaoqing.
Writing – review & editing: Wang xiaoqing.

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