Systematic Review and Meta-Analysis

Medicine

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Predictive value of platelet parameters for bronchopulmonary dysplasia in preterm infants

A systematic review and meta-analysis

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Abstract

Background: To systematically evaluate the predictive value of platelet (PLT) parameters for bronchopulmonary dysplasia (BPD) in preterm infants.

Methods: PubMed, Embase, Cochrane Library, and Web of Science databases were searched for studies on PLT parameters predicting BPD in preterm infants from inception to December 2023. The Newcastle-Ottawa Scale was adopted to judge the article's quality. RevMan 5.4 was utilized for Meta-analysis, and Stata/SE 15.1 was applied for sensitivity analysis and Egger regression test.

Results: Ten studies were included, including 1637 preterm infants, of which 540 were diagnosed with BPD. Meta-analysis showed that PLTs (SMD = –0.98, 95% CI [–1.57, –0.38], $P = .001$), mean platelet volume (MPV) (SMD = 0.67, 95% CI [0.19, 1.15], $P = .006$), and PMI (SMD = –0.47, 95% CI [–0.65, –0.28], $P < .00001$) could assist in predicting BPD in preterm infants. Subgroup analyses showed that PLT parameters 3 days after birth had better predictive performance for BPD in preterm infants. Sensitivity analysis implied no significant change in the results after excluding the studies 1 by 1, suggesting robust results of meta-analysis. There was a significant publication bias in the enrolled studies ($P < .001$).

Conclusion: PLT, MPV, and PMI have a predictive value for BPD in preterm infants.

Abbreviations: BPD = bronchopulmonary dysplasia, CI = confidence interval, MPV = mean platelet volume, PDW = platelet distribution width, PLT = platelet count, PMI = platelet mass index, SMD = standardized mean difference.

Keywords: bronchopulmonary dysplasia, meta-analysis, platelet parameters, preterm infants

1. Introduction

In 1967, Northway first defined children with bronchopulmonary dysplasia (BPD) as preterm infants who develop respiratory distress syndrome after prolonged ventilatory support.[1] BPD in preterm infants is typically characterized by airway damage and parenchymal fibrosis, leading to chronic respiratory failure and long-term oxygen demand, similar to chronic obstructive pulmonary disease in adults.[2,3] According to Jobe,[3,4] BPD in infants with very low-birth weight following the use of surfactant and prenatal steroids manifests as arrested alveolar and vascular development. This disruption of the developmental process occurs at or before the late tubular and saccular stages.[2,5] Preterm labor (gestational age < 37 weeks) is common, accounting for approximately 6% to 14% of pregnancies. Approximately 50,000 ultra-preterm infants are born each year in the U.S., and about 35% (18,000) of them develop BPD. The BPD incidence varies widely among centers (about 20% to 75%). The greatest risk factors for BPD are preterm birth and low-birth weight. Approximately 80% of preterm infants born at 22 to 24 weeks' gestation develop BPD, while approximately 20% of preterm infants born at 28 weeks' gestation develop BPD. Other perinatal risk factors include intrauterine growth restriction, male infants, chorioamnionitis, race or ethnicity, and smoking. Genetic factors may also contribute to the development of BPD.[6]

Currently, BPD is primarily diagnosed and classified based on the criteria published by the National Institute of Child Health and Human Development (NICHD) in 2001, i.e., for preterm infants born at <32 weeks' gestation with a cumulative postnatal oxygen use of 28 days. Corrected gestational age of

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Consent for publication is not applicable to this article.

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Ethics approval and consent to participate are not applicable to this article.

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36 weeks without oxygen inhalation, inhaled oxygen concentration < 0.30, inhaled oxygen concentration ≥ 0.30, or need for positive pressure ventilation and mechanical ventilation are defined as mild, moderate, and severe BPD.[7] Currently, the prediction of BPD is difficult, and there is still a lack of accurate predictive models for BPD in preterm and low-birth weight infants in clinical practice. Lefrançais E et al have unveiled that the lungs are implicated in platelet (PLT) biogenesis, producing about 50% of the total amount of PLTs per hour, i.e. 10 million PLTs.[8] They propose that the lung is a major site to produce terminal PLTs and an essential hematopoietic organ. Wang et al[9] suggest that lung lesions and abnormalities in microvessel morphology may influence PLT production from the lungs. Thereby, peripheral PLT parameters may change before and/or after BPD diagnosis and potentially predict BPD in preterm infants. Clinical retrospective studies by Dani and Bolouki Moghaddam[10,11] have found that mean platelet volume (MPV) could predict BPD, and Chen study[12] shows that higher PLTs are an independent index for moderate-to-severe BPD. However, Jiang et al[13] suggest that lower PLTs may increase the risk of BPD.

Although many clinical articles have analyzed the relationship between PLT parameters and BPD in preterm infants, evidence-based medicine is still lacking. No relevant meta-analyses and systematic evaluations have been published so far, and we are not yet sure whether PLTs-related parameters can accurately predict BPD. Therefore, this study was to conduct a meta-analysis to appraise the correlation between PLTs-related parameters and BPD and to further demonstrate their predictive value for BPD.

2. Methods

2.1. Ethics statement

This study is a systematic review and meta-analysis review, not human or animal experiments, so it does not require ethical approval from the ethics committee. This review was performed in alignment with the guidance provided by the Cochrane Handbook for Systematic Reviews of Interventions and strictly follows the criteria established in the 2020 PRISMA statement, an updated framework for reporting systematic reviews.

2.2. Literature search strategy

The study protocol was registered with PROSPERO (https://www.crd.york.ac.uk/PROSPERRO/#homepage) (No. CRD42024540625). PubMed, Embase, Cochrane Library, and Web of Science were searched from inception to December 2023 for English literature on PLT parameters predicting BPD in preterm infants. PLT parameters mainly included platelet count (PLT), MPV, platelet mass index (PMI), and platelet distribution width (PDW). The searches were conducted using a combination of subject terms and free words and were adjusted to the characteristics of each database. English search terms: "Blood Platelets," "Blood Platelet," "Platelet, Blood." "Platelets, Blood," "Thrombocytes," "Thrombocyte." "Platelets," "Platelet," "Bronchopulmonary Dysplasia." "Dysplasia, Bronchopulmonary," "BPD." The Pubmed search formula was as follows: (("Blood Platelets"[Mesh]) OR (((((((Blood Platelet) OR (Platelet, Blood)) OR (Platelets, Blood)) OR (Thrombocytes)) OR (Thrombocyte)) OR (Platelets)) OR (Platelet))) AND (("Bronchopulmonary Dysplasia"[Mesh]) OR ((Dysplasia, Bronchopulmonary) OR (BPD))). Detailed search formulas for the remaining databases are given in Table S1, Supplemental Digital Content, http://links.lww.com/MD/O237.

2.3. Literature inclusion and exclusion criteria

Inclusion criteria covered

(1) study type: published cohort study or case-control study;
(2) study subjects: preterm infants;
(3) using PLT parameters to predict BPD in preterm infants;
(4) categorizing the preterm infants into a BPD group (case group) and a non-BPD group (control group).

Articles were excluded for

(1) duplicates;
(2) non-English literature;
(3) incomplete data;
(4) without full text or access to full text;
(5) meeting abstracts, letters, comments, corrections, and responses;
(6) animal experiments;
(7) cellular experiments.

2.4. Literature quality assessment

The quality of enrolled articles was judged by the Newcastle-Ottawa Scale (NOS),[14] and studies with scores of 7 to 9 were of high quality.[15] The evidence level for each study was also judged based on the Oxford Center for Evidence-Based Medicine Levels of Evidence Working Group.[16] Two researchers independently assessed the quality and evidence level. Any discrepancies were addressed via discussion.

2.5. Data extraction

Data extraction was done independently by 2 researchers, with a third researcher making the final decision in case of disagreement. We extracted the following data from the enrolled articles: first author, year of publication, time of study, country of study, study design, sample size, age, time of specimen collection, PLT value, MPV value, PMI value, PDW value, gestational age, birth weight, and Apgar score. When continuous variables were depicted as median plus range or interquartile spacing, the mean ± standard deviation was computed using validated mathematical methods.[17,18] In case of missing or not reported data, we contacted the corresponding authors to obtain complete data, if available.

2.6. Statistical analysis

Evidence synthesis was done in Review Manager 5.4 (Oxford Cochrane Collaboration, UK). Comparisons of continuous and dichotomous variables were performed using WMD and OR for data merging, respectively. 95% confidence intervals (CIs) were reported for all indicators. Heterogeneity was judged by chi-square tests (χ^2) (Cochran Q) and I^2.[19] If marked heterogeneity was found (χ^2 P-value < 0.05 or $I^2 > 50\%$), a random-effects model was adopted to estimate the pooled WMD or OR. In addition, 1-way sensitivity analyses were done to ascertain the impact of the enrolled literature on the combined results with significantly heterogeneous outcomes. Funnel plots were created by Review Manager 5.4, and Egger test was conducted for results from 3 or more studies using Stata S/E 15.1 (Stata Corp, College Station)[20] for visual assessment of publication bias. Subgroup analyses based on testing time, region, sample size, and birth weight were performed to explore the variability of results between subgroups and potential sources of heterogeneity.

3. Results

3.1. Search results and included literature

806 articles were retrieved, 796 were excluded according to the eligibility criteria, and finally 10 articles were enrolled.[9–13,21–25] The literature screening process is displayed in Figure 1.

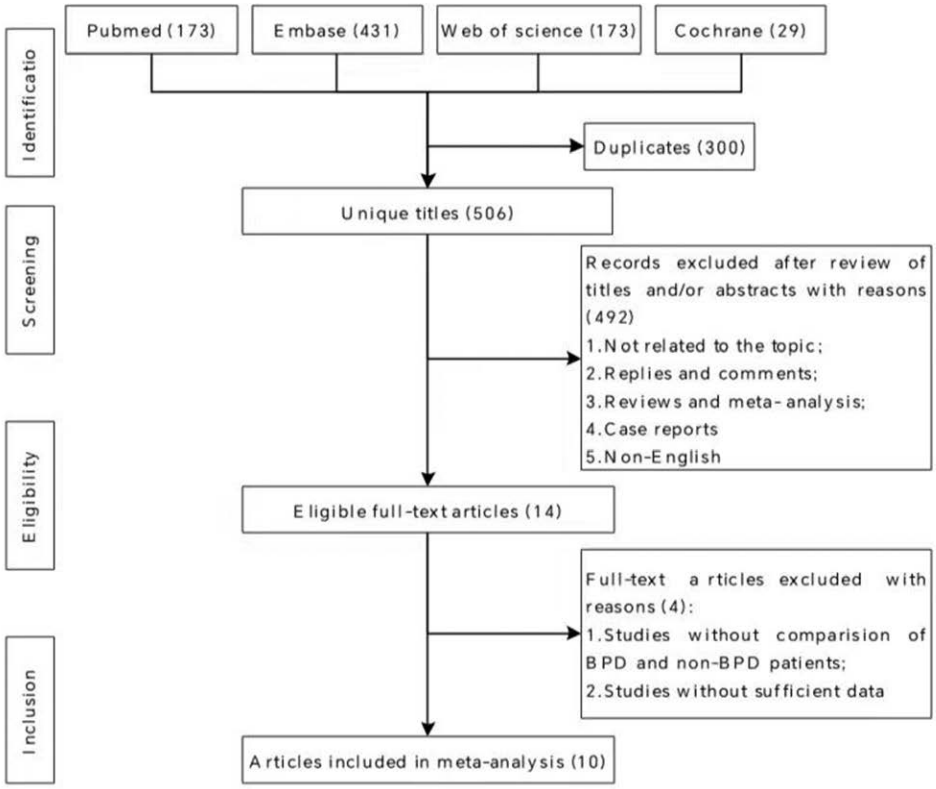

Figure 1. Flow diagram for study selection.

Table 1

Baseline characteristics of include studies.

Authors	Study period	Country	Study design	Time of platelet parameters measurement	BW (g)/GA (wk)	Patients (n) BPD/ Non-BPD	Platelet parameter	Quality score
Yan et al.	2017 to 2018	China	retrospective	Within 24 h of birth	1130.0/29.1	48/48	PLT	8
Jiang et al.	2017 to 2022	China	retrospective	Within 48 to 72 h of birth	1505.2/29.9	48/76	PLT + MPV + PDW + PMI + PLR	7
Cekmez et al.		Turkey	retrospective	28 d after birth	1126/.230.1	44/152	PLT + MPV	6
Wang et al.	2015 to 2019	China	retrospective	Within 24 h of birth	1227.4/28.3	64/70	PLT + MPV + PDW + PCT	8
Chen et al.	2016 to 2018	China	retrospective	Within 24 to 48 h of birth	827.3/31.9	60/55	PLT + MPV + PDW	7
Dani et al.	2003 to 2008	Italy	retrospective	Within 3 to 7 d of birth	923.8/27.0	57/153	PLT + MPV	8
Okur et al.	2012 to 2014	Turkey	retrospective	Within 48 h of birth	994/28	97/233	PLT + MPV + PMI	8
Bolouki et al.	2011 to 2015	Iran	retrospective	Within 72 h of birth	1495.5/29.7	30/30	MPV	7
Shamsollah et al.	2008 to 2012	Iran	retrospective	Second week after birth	1707.4/31.9	30/250	PLT + MPV	6
Sunil et al.	2017 to 2020	The USA	retrospective	Within 24 h of birth	1024.7/28.2	62/30	PLT + MPV + PMI	8

* BPD = bronchopulmonary dysplasia, BW = birth weight, GA = gestational age, MPV = mean platelet volume, PDW = platelet distribution width, PLT = platelet count, PMI = platelet mass index.

3.2. Basic characteristics and quality evaluation results

10 included studies involved 1637 preterm infants, of which 540 preterm infants were diagnosed with BPD. All 10 included studies revealed that the mean birth weight and gestational age of BPD infants were greatly lower than that of non-BPD infants. 9 studies reported the diagnostic efficacy of PLT, 9 reported MPV, 3 reported PMI, 3 reported PDW, 1 reported PLR, and 1 reported PCT. The article quality was moderate to high, with NOS scores of 6 to 8. The basic characteristics and quality of enrolled studies are displayed in Table 1.

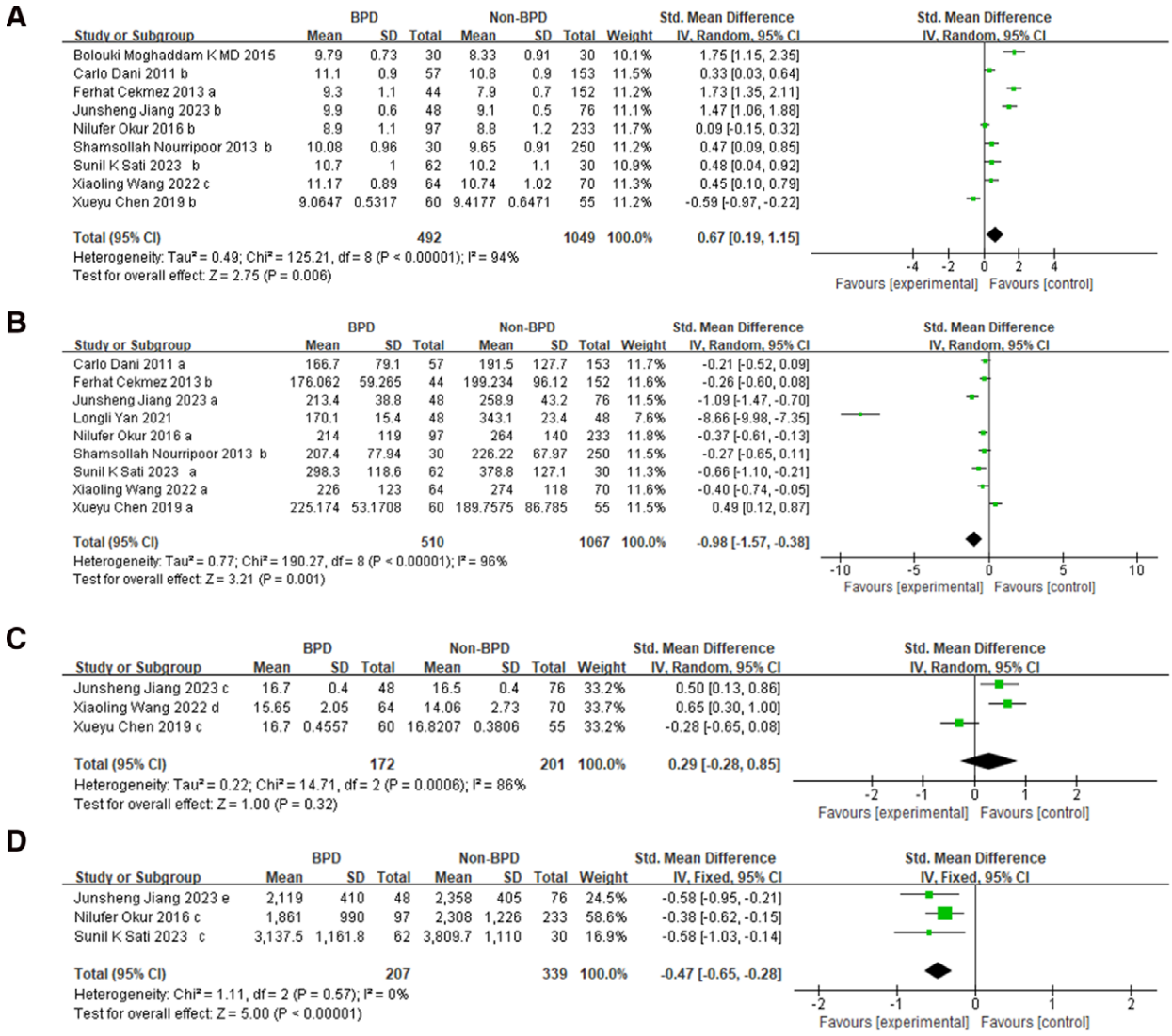

Figure 2. Forest plots of platelet parameters: (A) MPV, (B) PLT, (C) PDW, (D) PMI. MPV = mean platelet volume, PDW = platelet distribution width, PLT = platelet count, PMI = platelet mass index.

3.3. Results of meta-analysis

For MPV, 9 papers[9–13,21–24] containing 1541 preterm infants were included. MPV levels were markedly higher in BPD patients than in the non-BPD group (SMD = 0.67, 95% CI [0.19, 1.15], $P = .006$), with $I^2 = 94\%$ (Fig. 2A). The funnel plot suggested symmetry (Fig. 3B), and Egger test suggested no publication bias ($P = .139$).

For PLT, meta-analysis included 9 papers[9,10,12,13,21–25] with 1577 preterm infants. PLT levels were notably lower in BPD patients than in the non-BPD group (SMD = −0.98, 95% CI [−1.57, −0.38], $P = .001$), with $I^2 = 96\%$ (Fig. 2B). The funnel plot suggested symmetry (Fig. 3A), and the Egger test implied publication bias ($P = .017$).

For PMI, meta-analysis included 3 papers[13,23,24] with 546 preterm infants. PMI levels were greatly lower in BPD patients than in the non-BPD group (SMD = −0.47, 95% CI [−0.65, −0.28], $P < .00001$), with $I^2 = 0\%$ (Fig. 2D). The funnel plot suggested symmetry (Fig. 3C), and the Egger test suggested no publication bias ($P = .017$).

For PDW, meta-analysis included 3 papers[8,11,12] with 373 preterm infants. PDW was not statistically different in BPD patients relative to the non-BPD group (SMD = 0.29, 95% CI [−0.28, 0.85], $P = .32$), with $I^2 = 86\%$ (Fig. 2C).

3.4. Sensitivity analysis

The statistical results noted that excluding anyone literature, the results were still statistically significant, indicating that MPV, PLT, and PMI were stable, and the results were credible for the prediction of BPD in preterm infants (Fig. 4).

3.5. Subgroup analysis

Subgroup analysis was performed for PLT and MPV, and the main indicators included the testing timing, region, sample size, and birth weight (Table 2). The results evinced that PLT had better predictive power for BPD in preterm infants when blood specimens were collected ≥ 72 h after birth, and the testing timing did not significantly affect the prediction of BPD in preterm infants by MPV. In addition, subgroup analysis revealed that testing timing was not the main reason for high heterogeneity of PLT and MPV in predicting BPD in preterm infants. PLTs had better predictive power for BPD in preterm infants in Asian regions than non-Asian regions, and regions did not affect the prediction of BPD by MPV. The heterogeneity analysis suggested that geographic variation was a cause for high heterogeneity in the prediction of BPD in preterm infants by MPV rather than by PLTs. The difference in sample size was a cause for higher

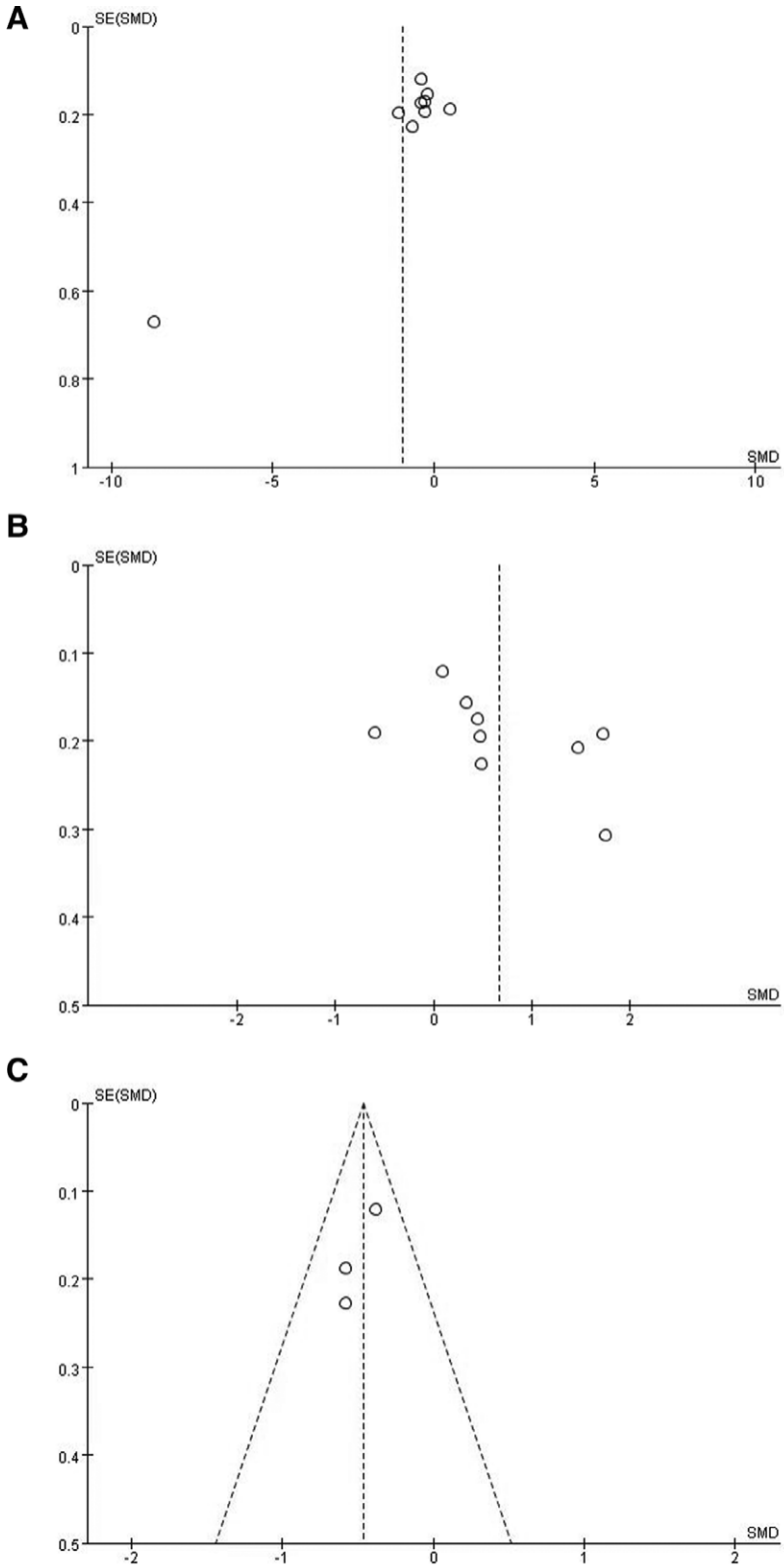

Figure 3. Funnel plots of platelet parameters: (A) PLT, (B) MPV, (C) PMI. MPV = mean platelet volume, PLT = platelet count, PMI = platelet mass index.

heterogeneity of BPD in preterm infants predicted by PLT rather than MPV. PLT and MPV had better predictive value for BPD in preterm infants with birth weight of >1,000 g, and birth weight was a cause for higher heterogeneity of BPD in preterm infants predicted by PLT and MPV. BPD had better predictive value, and birth weight was a cause for higher heterogeneity of BPD in preterm infants predicted by PLT and MPV (Table 2).

4. Discussion

Currently, the most used diagnostic criteria for diagnosing BPD are those published by the NICHD in 2001: i.e., the need for oxygen support (inhaled oxygen concentration FIO2 > 21%) after preterm delivery for more than 28 days cumulatively. In 2018, the NICHD proposed a new diagnostic criterion, i.e., preterm infants with < 32 weeks' gestation with persistent

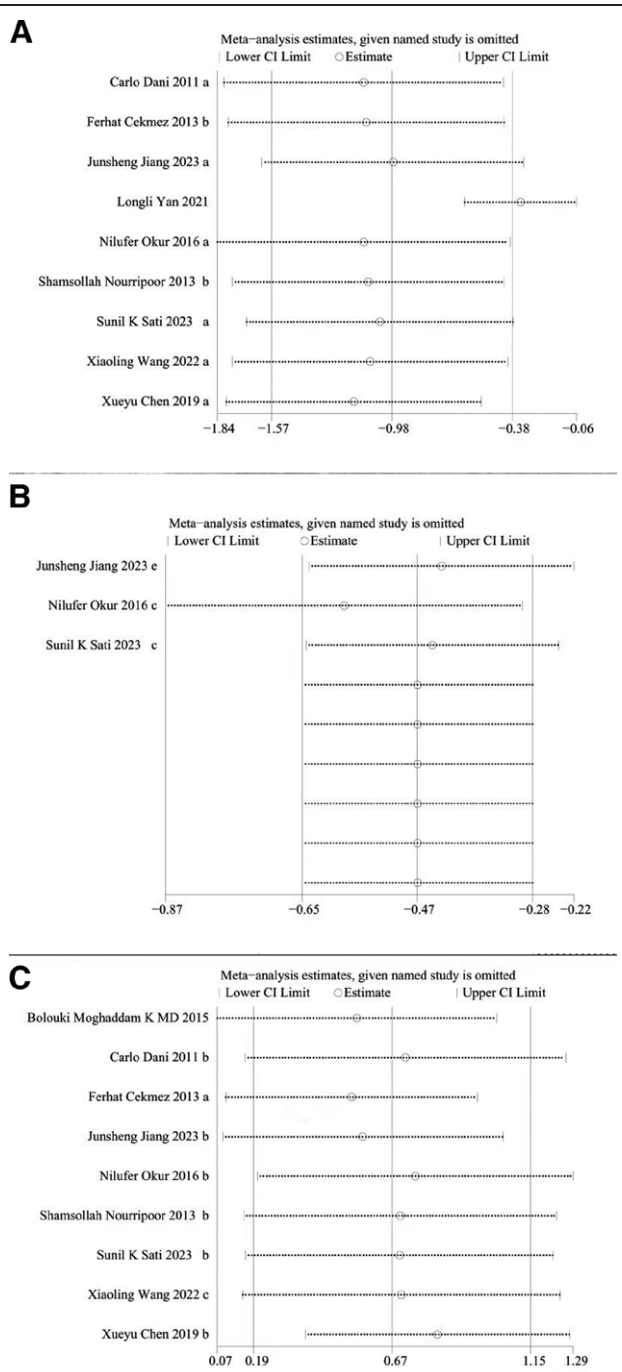

Figure 4. Sensitivity analysis of platelet parameters: (A) PLT, (B) PMI, (C) MPV. MPV = mean platelet volume, PLT = platelet count, PMI = platelet mass index.

parenchymal lung pathology confirmed by imaging and oxygen therapy support (more than 3 days consecutively) 36 weeks post-menstrual age to maintain arterial oxygen saturation at 90% to 95%. There is a time lag in BPD diagnosis in preterm infants by both new and old criteria. It may not be possible to diagnose BPD early and accurately by existing diagnostic criteria due to age and testing technology. Many studies[26–28] manifest that PLTs are closely related to the lungs and that PLTs may be the effector cells in pulmonary fibrosis diseases and chronic pulmonary vascular syndromes. Early prediction of BPD has the potential to allow physicians to use more active treatment regimens to benefit preterm infants at high risk for BPD.

Due to the simplicity and lower cost of obtaining blood specimens, PLT-related parameters have predictive value for BPD in preterm infants. Nilufer Okur[24] found that preterm infants with BPD had lower PMI levels in the early postnatal period than preterm non-BPD infants. Shamsollah et al[22] pointed out that in the first 3 postnatal days, higher MPV is a possible factor for BPD in preterm infants, possibly because high MPV may predispose neonates to inflammation and oxidative lung injury. Although many studies have investigated the predictive power of different PLT parameters for BPD in preterm infants, the present article is the first meta-analysis to assess the predictive performance of different PLT parameters for BPD in preterm infants.

Meta-analysis was carried out for 4 indicators: PLT, MPV, PMI, and PDW. We found that PLT, MPV, and PMI had predictive value for BPD in preterm infants; the lower the values of PLT and PMI, the higher the probability of BPD in preterm infants, and the higher the value of MPV, the lower the probability of BPD in preterm infants. The stability of the predictive power of PLT, MPV, and PMI for BPD in preterm infants was further confirmed by sensitivity analysis. The funnel plot and Egger test implied publication bias in the PLT-assisted diagnosis of BPD in preterm infants, while there was no publication bias in MPV and PMI. PLTs are usually viewed as small cytoplasmic fragments from mature megakaryocytes in the bone marrow, participating in diverse physiological processes. Megakaryocytes are the mother cells responsible for PLT production and predominantly located in the lungs and pulmonary vascular beds of mammals.[29] PLTs in the posterior pulmonary vasculature are visibly higher than in the pulmonary arteries,[28] indicating that the lungs are the site of PLT production. The lungs in humans and other mammals serve as storage sites for PLTs, which are released upon certain stimuli.[27] Lefrançais et al unraveled that the lungs are the primary location for PLT biogenesis and contributed about half of total PLTs.[8] Many studies in adults have noted that lung injury and lung diseases, like cystic fibrosis, tuberculosis, asthma, and pulmonary hypertension are connected with a decrease in circulating blood PLTs.[30–33]

BPD is a prevalent chronic inflammatory lung disorder in very low-birth weight and very preterm infants, linked to delayed lung growth and microvascular dysplasia.[27] Altering the morphology of the pulmonary capillary bed can disrupt the distribution or steps of lung megakaryocyte fragmentation. This paper illustrated that PLT levels in BPD preterm infants were substantially lower than those in non-BPD preterm infants, and PLT levels 3 days after birth had better predictive value for BPD in preterm infants. A study discovered that PLT parameters were not related to BPD in preterm infants on the first postnatal day.[34] Consistently, our findings evinced that PLT levels in BPD and non-BPD preterm infants did not differ notably in the early postnatal period. No studies have been conducted to elucidate the possible mechanisms. Okur et al[24] measured PLT parameters on the day of birth and 3 to 7 postnatal days and found that PLT levels were higher than on the day of birth in both BPD and non-BPD groups on 3 to 7 postnatal days. However, Dani et al[10] measured PLT parameters at the time of birth and 24 to 48 hours after birth and found that PLT levels were higher at birth than at 24 to 48 hours after birth in both BPD and non-BPD groups. Therefore, we cannot judge the likelihood of BPD in preterm infants simply based on PLT counts at different time points after birth, because PLT destruction and activation occur simultaneously. However, we hypothesized that preterm infants comorbid with adverse events have less inflammatory oxidative stress in the early postnatal period, and the process of PLT destruction and activation is relatively weak. These findings further manifest that PLT biosynthesis is affected by BPD.

Chronic inflammation during BPD may increase megakaryocyte depletion and destruction. Additionally, pulmonary arrest and microvascular dysplasia in BPD affect PLT biosynthesis and release, leading to a reduction in circulating PLTs.[35] MPV is inversely proportional to PLTs.[36] Under certain unfavorable conditions, PLTs are destroyed in the peripheral circulation, and the body initiates

Table 2

Subgroup analysis of PLT and MPV.

	PLT				MPV			
Subgroup	**Study**	**SMD (95% CI)**	***P* value**	**I^2**	**Study**	**SMD (95% CI)**	***P* value**	**I^2**
Total	9	−0.98 (−1.57, −0.38)	.001	96%	9	0.67 (0.19, 1.15)	.006	94%
Timing of testing								
≥72 h	4	−2.25 (−3.69, −0.82)	.002	98%	3	0.30 (0.02, 0.57)	.03	52%
<72 h	5	−0.27 (−0.72, 0.19)	.26	88%	6	0.85 (0.11, 1.58)	.02	95%
Region								
Asia	7	−1.21 (−1.99, −0.43)	.002	97%	7	0.75 (0.13, 1.37)	.02	95%
Non-Asia		−0.40 (−0.84, 0.03)	.07	62%	2	0.38 (0.13, 0.63)	.003	0%
Sample size								
≥150	4	−0.29 (−0.44, −0.14)	.0001	0%	4	0.65 (−0.03, 1.32)	.06	94%
<150	5	−1.85 (−3.20, −0.51)	.007	98%	5	0.69 (−0.09, 1.48)	.08	94%
Birth weight								
≥1000 g	6	−1.62 (−2.59, −0.66)	.001	97%	6	1.04 (0.52, 1.57)	<.0001	90%
<1000 g	3	−0.05 (−0.52, 0.43)	.85	87%	3	−0.04 (−0.52, 0.43)	.85	86%

* CI = confidence interval, MPV = mean platelet volume, PLT = platelet count, SMD = standardized mean difference.

a compensatory mechanism by stimulating the productive function of PLTs and releasing immature PLTs. Immature/premature PLTs encompass more proteins, enzymes, and particles, with active metabolism, larger size, and more heterogeneity.[9] Higher MPV may worsen respiratory distress syndrome by inhibiting surfactants, thus favoring BPD.[10] Platelet mass index (PMI) is associated with PLT function. PMI (PLT multiplied by MPV) may also be a better inflammatory parameter than MPV in preterm infants because PMI combines both PLT and MPV. However, there are relatively few studies on PMI and BPD in preterm infants, and further research is warranted to elucidate the link between them. Through subgroup analysis, we also found that both PLT and MPV had a better predictive value for BPD in preterm infants with birth weight > 1000 g, which was contrary to many studies pointing out that BPD children have lower birth weight than non-BPD children. We speculate that the subgroups were classified according to birth weight only, and we did not consider and exclude the effects of gestational age, other common preterm complications, testing timing of blood parameters, and underlying diseases during the mother's pregnancy on the infant's birth weight. Therefore, further studies are needed to validate this conclusion.

There are some limitations: significant heterogeneity was observed in the enrolled studies, which may reduce the robustness of the findings despite the use of random-effects models; due to the limited number of enrolled literature, studies with significant heterogeneity remaining after subgroup analyses were not analyzed; and significant publication bias was found, which may be related to the easy publication of positive results and large differences in sample sizes of enrolled studies. The results in this article were derived from case-control studies and lacked confirmation from prospective cohort studies. Thus, further studies are needed to elucidate the exact predictive value of PLT parameters for BPD.

In summary, this study illustrates that PLT, MPV, and PMI have predictive values for BPD in preterm infants and that low PLTs, low PMI, and high MPV may suggest that preterm infants are at risk for BPD. Nonetheless, large prospective studies are required to confirm the predictive value of PLT parameters for BPD in preterm infants due to the significant heterogeneity, publication bias, and the type of original studies.

Author contributions

Conceptualization: Chonghai Liu.
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Methodology: Shunyou Zhang.
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Software: Shunyou Zhang, Yulin He.
Supervision: Chonghai Liu.
Validation: Chonghai Liu.
Visualization: Chonghai Liu.
Writing – original draft: Shunyou Zhang.
Writing – review & editing: Shunyou Zhang.

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