Prediction Models for Bronchopulmonary Dysplasia in Preterm Infants: A Systematic Review and Meta-Analysis

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Objective To review systematically and assess the accuracy of prediction models for bronchopulmonary dysplasia (BPD) at 36 weeks of postmenstrual age.

Study design Searches were conducted in MEDLINE and EMBASE. Studies published between 1990 and 2022 were included if they developed or validated a prediction model for BPD or the combined outcome death/BPD at 36 weeks in the first 14 days of life in infants born preterm. Data were extracted independently by 2 authors following the Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies (ie, CHARMS) and PRISMA guidelines. Risk of bias was assessed using the Prediction model Risk Of Bias ASsessment Tool (ie, PROBAST).

Results Sixty-five studies were reviewed, including 158 development and 108 externally validated models. Median c-statistic of 0.84 (range 0.43-1.00) was reported at model development, and 0.77 (range 0.41-0.97) at external validation. All models were rated at high risk of bias, due to limitations in the analysis part. Meta-analysis of the validated models revealed increased c-statistics after the first week of life for both the BPD and death/BPD outcome.

Conclusions Although BPD prediction models perform satisfactorily, they were all at high risk of bias. Methodologic improvement and complete reporting are needed before they can be considered for use in clinical practice. Future research should aim to validate and update existing models. *(J Pediatr 2023;258:113370)*.

See editorial, p 113389

Despite recent advances in perinatal care, bronchopulmonary dysplasia (BPD) remains a frequent complication of very preterm birth.[1] It is associated with greater odds of mortality, respiratory morbidity, adverse neurologic development, and increased health care–related costs.[2-4]

Identifying the development of BPD at an early stage is important to improve treatment of high-risk infants and provide sufficient long-term prognostic information to parents.[5] A systematic review published in 2013 identified BPD prediction models developed using routinely collected clinical data during the first week of life.[6] Most of the publications reported the model discrimination, which is a key performance measure recommended in the TRIPOD (ie, Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis) Statement.[7] However, none reported calibration, and external validation was rarely performed. Finally, no standardized tool to evaluate the risk of bias (RoB) in prediction models was available at the time of that review, and thus their quality has not been evaluated formally. Several new prediction models have since been published, including models investigating potential biomarkers. Furthermore, the Prediction model Risk Of Bias ASsessment Tool (ie, PROBAST) now provides a formal RoB assessment for studies aiming to develop or validate a prediction model.[8] Thus, our objective was to provide a systematic review of multivariable prediction models for BPD at 36 weeks of postmenstrual age (PMA) in infants born preterm and assess their RoB.

95% PI	95% prediction interval
BPD	Bronchopulmonary dysplasia
PMA	Postmenstrual age
PROBAST	Prediction model Risk Of Bias ASsessment Tool
RoB	Risk of bias

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Methods

This systematic review was performed and reported according to the Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modeling Studies (CHARMS) and the PRISMA guidelines (**Appendix 2**; available at www.jpeds.com).[9,10] Identification of eligible studies for inclusion was performed by using the MEDLINE and EMBASE electronic databases restricted to articles published between January 1, 1990, and July 31, 2022. The search strategy consisted of key words and medical subject headings terms under the topic of prediction model, BPD, and newborn (eMethods in the **Appendix 1**; available at www.jpeds.com). No language restrictions were applied. The protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO, registration number: CRD42021249437).

All studies that aimed to develop or validate a multivariable prediction model for BPD or the combined outcome death or BPD (death/BPD) in the first 14 days of life after preterm birth were eligible for inclusion. Additional eligibility criteria were that BPD assessment had to be performed at 36 weeks of PMA; studies with earlier BPD definitions were excluded. Studies had to use data from infants born after 1990, as antenatal steroids and surfactant treatment were not widely implemented in infants born before 1990. Finally, reviews, guidelines, conference abstracts, and animal studies were excluded. There was no restriction on the predictors considered for inclusion in the models, including clinical data, biomarkers, imaging results, or other information.

Data Extraction and Analysis

Screening and identification of the studies were independently performed by 2 authors. Titles and abstracts were screened to determine eligibility. A full-text review was performed for all potentially eligible studies to determine inclusion or exclusion. Data from the included studies were independently extracted in duplicate by 2 authors in accordance with the CHARMS checklist[9] (eMethods in **Appendix 1**). Disagreement or differences were resolved by consensus or by a third reviewer. Authors of the included studies were not contacted to obtain additional data.

Characteristics of the included studies, development models, and externally validated models were described. For models that were both developed and validated in the same study, information on development and validation was extracted separately. Participants and predictors data were summarized with medians and ranges. The number of events per variable was calculated for each development model by dividing the number of outcome events—or the number of infants without the outcome if such was lower—by the number of candidate predictors. The median c-statistic and range were calculated separately for development models (apparent c-statistic when it was the only available information and c-statistic corrected for optimism when reported) and for externally validated models.

Externally validated prediction models were analyzed quantitatively by using random effects meta-analyses for the outcomes BPD and death/BPD separately in order to quantify an overall performance, including a prediction interval and heterogeneity of these models over time. Only discrimination performances, ie, c-statistics, were meta-analyzed, as calibration performances were poorly reported. If researchers performed external validation of several models very similar to each other (eg, one variable coded as continuous in the first model and dichotomized in the second model) at the same time point, only the best c-statistic was included. Meta-analysis was performed using the actual reported c-statistic including SE and/or 95% CI reported in the included study. These values were logit transformed, which resulted in a pooled c-statistic with corresponding 95% CI.[11] In addition, 95% prediction intervals (PIs) were calculated to provide boundaries on the likely performance in future model validation studies that are comparable with the studies included in the meta-analysis.[12] We then stratified the meta-analysis by timing assessment (birth to 24 hours of life, day 1 to day 7, and day 8 to day 14). The prespecified minimum number of models to perform meta-analysis was 3, this number was met for each outcome and each time point.

RoB and Applicability Assessment

The RoB and applicability assessment was evaluated independently by 2 authors using the PROBAST guidelines.[8] The RoB and applicability for each domain was scored as low, high, or unclear. If any of the signaling questions in a domain was answered with "no," the risk of bias of that domain was scored as high, and eventually, the overall judgment was scored as high risk of bias.

Results

The search resulted in 11 260 references (**Figure 1**). Duplicates (n = 3298), reviews, editorial papers, and irrelevant studies based on their title (n = 5239) were excluded. Of the remaining 2723 abstracts, 683 full texts were retained for review. Of these, 618 references were excluded for various reasons (**Figure 1**). Finally, 65 studies met the inclusion criteria.[13-75] One study that performed external validation and reported calibration plots for several BPD prediction models was excluded because data was used from infants born before 1990.[6]

Forty-nine studies described the development of at least 1 model, accounting for 158 developed models in total. Thirty-two studies externally validated at least 1 model accounting for 108 models. From those 32 studies, 9 externally validated a model that had been developed in the same paper.[13,14,16,21,22,28,30,64,67] Finally, 12 studies developed at least 1 model and externally validated existing models.[16,18,21,50,52,57,58,60,62,63,68,71]

The study characteristics of the 65 included studies are described in **Table I**). The included studies were published

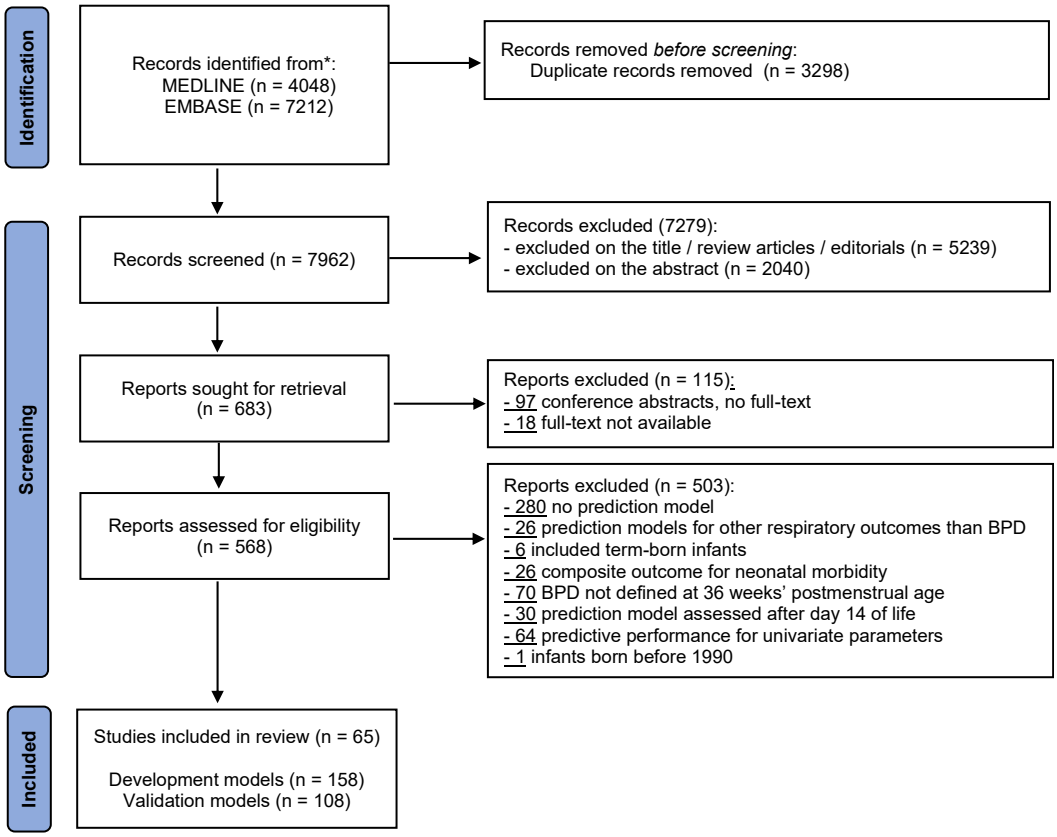

Figure 1. Flow diagram. *BPD*, bronchopulmonary dysplasia.

between 1996 and 2022, and the number of publications increased over time. Almost one-half of the included studies were performed in North America, followed by Europe. Most of the studies included data from single centers. Participants included in development and validation samples were similar for median gestational age (27.2 and 28.0 weeks, respectively), and median birth weight (911 and 938 g, respectively).

Development of BPD Prediction Models

Model Development. The total number of eligible infants was reported in most models (99.4%) (**Table II**). However, the total number of analyzed infants was less frequently reported (89.2%) and ranged from 43.8% to 100% of eligible infants. Some of the studies with high numbers of eligible infants did not report how many infants were finally analyzed in the models,[28,30,43,46] which explains the discrepancy between the median number of the analyzed infants and of outcome events. The proportion of infants with BPD from the total number of analyzed infants ranged from 14.8% to 68.2% across the studies and with death/BPD from 31.3% to 77.0%. The median number of predictors considered for inclusion in the models was 15 (range 1-50). The number of events per variable was less than 10 in 33.6%, and more than 20 in 40.9% of the models. The final prediction models included a median of 6 predictors (range 2-21). The predicted outcome was either BPD (43.7%) or death/BPD (56.3%) 36 weeks of PMA (**Table I**). Infants that died before 36 weeks of PMA were either excluded from analyses (39.2%), included in the no-BPD group (0.6%),[13] or included in the death/BPD group (52.5%). The most frequent timing of model assessment was day 7 (31.0%).

As shown in **Table II**, most models used all candidate predictors before multivariable modeling (56.3%). Logistic regression with all predictors forced in the model was the most frequently used modeling method. Five models (3.2%) used Classification and Regression Tree analysis. In 55 models (34.8%), eligible participants with missing data were excluded from the analysis, and 52 models (32.9%) performed single or multiple imputation for imputation of missing data. For all other models, insufficient or no information was reported to determine how much missing data there was, and how it was handled. In some models, continuous predictors were converted into categories (7.6%).

Model Validation and Performance. Internal validation was performed in 78 models (49.4%) with single random split-sample of participant data (9.5%), cross-validation (35.4%), or resampling of same data set (4.4%) (**Table II**). For 17 models (10.8%), both development and external validation were described in the same article.[13,14,16,21,22,28,30,64,67] C-statistic was reported for most models (91.8%) with a median apparent c-statistic

Table I. Description of included studies

First author	Year of publication, country	Period of data collection	Study design	Inclusion criteria	Number of participants eligible/analyzed	Number of outcome events	Gestational age, wk, mean (SD) or median [IQR]	Birth weight, g, mean ± SD or median [IQR]	Timing of model assessment	Defined outcome
Development studies										
Ahmed[70]	2022, USA	1997-2015	Nested case–control, single center	Gestational age <29 wk	42/42	21	25.9 (1.18)	809 (175)	Before 72H	Moderate/severe BPD supplemental oxygen at 36 weeks of PMA
Alonso-Ojembarrena[71]	2022, Spain	2017-2021	Case–control, multicenter (n = 2)	Gestational age <32 wk	199/133	27	no BPD group 30 [29-31] BPD group 27 [25-29]	no BPD 1300 [1100-1445]; BPD 905 (620-1000)	D1, D3, D7, D14	Moderate/severe BPD: any respiratory support at 36 weeks of PMA
Greenberg[72]	2022, USA	2011-2017	Prospective cohort, multicenter (n = 38)	Gestational age $23^{0/7}$ to $28^{6/7}$ wk; BW 501-1250 g;	9843/9181	BPD grade 1 2 795; grade 2 1 526; grade 3 551; death 1052	25.9 (1.57)	850 (192)	D1, D3, D7, D14	Grade 1 BPD/grade 2 BPD/grade 3 BPD/death according to the 2019 definition by Jensen
Kindt[73]	2022, Germany	No information	Prospective cohort, single center	Gestational age <32 wk	55/52	13	27.2 (range 23.2–30.6)	798 [510–1590]	First week	Moderate or severe BPD according to NICHD 2001 definition
Umapathi[74]	2022, USA	No information	Prospective cohort, single center	Gestational age <32 wk	101/98	34	28.9 (1.91)	122 (319)	First week	Moderate/severe BPD or death: supplemental oxygen at 36 weeks of PMA
Zayat[75]	2022, Europe	2011-2012	Prospective cohort, multicenter (n = 19 regions from 11 countries)	Gestational age $24^{0/7}$ to $29^{6/7}$ wk	3662/3407	901	28 [26-29]	1000 (IQR 810-1200)	D14	Moderate/severe BPD: supplemental oxygen or respiratory support at 36 weeks
Aldecoa-Bilbao[57]	2021, Spain	2018-2020	Prospective cohort	Gestational age $23^{0/7}$ to $30^{6/7}$ wk	152/89	23	28.1 [26.7-29.8]	BPD: 856 (284) No BPD: 1077 (320)	D7	Moderate/severe BPD: supplemental oxygen or positive pressure ventilation at 36 WG
Alonso-Ojembarrena[52]	2021, Spain	2017-2020	Prospective cohort, multicenter (n = 6)	Gestational age <32 wk	356/298	73	29 [26-30]	1100 [859-1340]	D0, D3, D7, D14	BPD at 36 WG - physiologic definition (Walsh test)
Baud[58]	2021, Europe, USA	2008-2014	Randomized trial participants, multicenter (n = 21)	Gestational age $24^{0/7}$ to $27^{6/7}$ wk	523/523	232	26.5 [25.7–27.1]	840 (735–970)	At birth	Death or moderate/severe BPD: respiratory support at 36 WG, physiologic test if FiO_2 22-29%
Dai[59]	2021, China	2017-2019	Nested case–control, single center	Gestational age <32 wk	254/245	67	29.1 [27.9-30.6]	1200 [1020-1410]	Unclear	Death due to respiratory insufficiency or severe BPD (NICHD definition)
Gerull[60]	2021, Switzerland	2013-2017	Prospective cohort, multicenter (n = 2)	Gestational age <32 wk	523/229	26	29.6 [27.0-30.7]	1150 [840-1410]	D7	Death/BPD at 36 weeks

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Table I. Continued

First author	Year of publication, country	Period of data collection	Study design	Inclusion criteria	Number of participants eligible/analyzed	Number of outcome events	Gestational age, wk, mean (SD) or median [IQR]	Birth weight, g, mean ± SD or median [IQR]	Timing of model assessment	Defined outcome
Khurshid[61]	2021, Canada	2016-2018	Registry data, multicenter (n = 31)	Gestational age <33 wk	12 990/9006 (day 1) to 3899 (day 14)	3188	BPD/death group: 26.5 (2.4); survival without BPD group: 29.5 (2.1)	Not reported	D1, D7, D14	Death/BPD: supplemental oxygen or positive pressure ventilation at 36 WG
Liu[62]	2021, China	2019-2020	Prospective cohort, single center	Gestational age <32 wk	130/130	50	29.2 (1.8)	1195 (209.8)	D1, D2, D3, D6, D9, D12	BPD: 2019 definition by Jension
Mohamed[63]	2021, Canada	2019-2020	Prospective cohort, multicenter (n = 2)	Gestational age <29 wk	223/152	87	25.8 (1.5)	923 (250)	D3, D7, D14	BPD: supplementation of oxygen or respiratory support at 36 WG
Shim[64]	2021, South Korea	2013-2016	Registry data, multicenter (n = 66)	Unclear	6969/4600	1370	BPD 0 30.61 (1.80); BPD 1 27.49 (1.84); BPD 2 27.37 (2.18); BPD 3 26.64 (2.34)	BPD 0 127(174); BPD 1 1058 (23′); BPD 2 1025 (24); BPD 3 886 (264)	D0	Moderate and severe BPD: NIH definition
Song[65]	2021, China	2016-2021	Retrospective cohort, single center	Gestational age <32 wk; BW <1500 g	564/556	138	29.6 [28.6-30.5]	1200 [1050-1350]	D7	Moderate/severe BPD or death: NIH definition
Soullane[66]	2021, Canada	2015-2018	Retrospective cohort, single center	Gestational age $23^{0/7}$ to $28^{6/7}$ wk	191/191	98	BPD/death 26 [24,26]; no BPD 27 [25,28]	BPD/death 760 [633 888]; no BPD 950 [750, 1170]	D10	BPD: supplemental oxygen or respiratory support at 36 wk or at discharge.
Ushida[67]	2021, Japan	2006-2015	Registry data, multicenter (n = 200)	Gestational age <32 wk; BW <1500 g	33 690/20 771	4986	27.8 (2.5)	975 (299)	D0	BPD: oxygen requirement at 36 wk
Woods[68]	2021, Australia	2017-2018	Prospective cohort, single center	Gestational age <28 wk	125/96	46	26.4 (range 23.1-27.6)	855 (range 450-1390)	D1, D3, D7	Moderate/severe BPD: respiratory support at 36 wk
Zhang[69]	2021, China	2019-2021	Retrospective cohort, single center	Gestational age <32 wk; BW <1500 g	414/414	98	BPD group 28.8 (27.9, 30.0); non-BPD group 29.6 (28.7, 30.7)	BPD 1045.0 (923.8, 1222.5); no-BPD 1240.0 (1102.5, 1360.0)	D3, D7, D14	BPD: 2019 definition by Jensen
Sharma[54]	2020, USA	2011-2017	Retrospective cohort, single center	Gestational age 23-$26^{6/7}$ wk	317/263	155	No/mild BPD 26.0 (1.1) Moderate or severe BPD 24.7 (1.3)	No/mild BPD 918 (174); Moderate or severe BPD 727 (169)	D14	Moderate or severe BPD: >28 days supplemental oxygen and supplemental oxygen and/or positive pressure respiratory support confirmed by physiological test at 36 weeks of PMA or at time of discharge.

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Table I. Continued

First author	Year of publication, country	Period of data collection	Study design	Inclusion criteria	Number of participants eligible/analyzed	Number of outcome events	Gestational age, wk, mean (SD) or median [IQR]	Birth weight, g, mean ± SD or median [IQR]	Timing of model assessment	Defined outcome
Alvarez-Fuente[51]	2019, Spain	2014-2016	Prospective cohort, multicenter (n = 5)	Gestational age <28 wk; BW <1250 g	47/47	22	26 [25-27]	871 (161)	D7	Moderate or severe BPD: >28 days supplemental oxygen or respiratory support at 36 weeks of PMA. Deaths between D7 and D28 considered as severe BPD.
Beltempo[50]	2019, Canada	2010-2015	Retrospective cohort, multicenter (n = 30)	Gestational age 22-28$^{6/7}$ wk	9240/7975	2959	27 [unclear]	953 (244)	H12	BPD: oxygen supplementation at 36 weeks of PMA or at time of discharge.
Fairchild[49]	2019, USA	2009-2014	Retrospective cohort, single center	Gestational age 23-33 wk; BW <1500g	502/Unknown	187	28 [25-29]	1020 [800-1250]	D7	Death or BPD: oxygen supplementation or respiratory support at 36 weeks of PMA
Valenzuela-Stutman[46]	2019, Argentina, Chile, Paraguay, Peru, Uruguay	2001-2015	Prospective cohort, multicenter (n = 15)	BW 500-1500g	16 407/Unknown	2580/6121	29 (2.9)	1099 (275)	D1, D3, D7, D14	4 models with outcome moderate or severe BPD >28 days supplemental oxygen/CPAP or mechanical ventilation at Jenison 36 weeks of PMA; 4 models with outcome moderate or severe BPD/death at 36 weeks of PMA
Veneroni[45]	2019, Sweden	2011-2014	Prospective cohort, single center	Gestational age <28 wk	Unknown/22	15	24.6 (1.6)	653 (170)	D1	BPD: oxygen supplementation at 36 weeks of PMA
Bentsen[44]	2018, Norway	2016-2016	Prospective cohort, single center	Gestational age <28 wk	40/33	18	No/mild BPD 26.2 (1.1); Moderate or severe BPD 25.5 (1.3)	No/mild BPD 864 (164); Moderate or severe BPD 754 (154)	D2	Moderate or severe BPD according to NICHD definition
Boghossian[43]	2018, USA and Puerto Rico	2006-2014	Prospective cohort, multicenter (n = 852)	Gestational age <30 wk	156 587/Unknown		No information	No information	At birth	Moderate or severe BPD: oxygen supplementation at 36 weeks of PMA or at time of discharge
Sullivan[41]	2018, USA	2009-2015	Retrospective cohort, multicenter (n = 2)	BW <1500 g	778/730	186	28.0 (2.8)	1029 (298)	D7	Moderate or severe BPD: oxygen supplementation at 36 weeks of PMA
Kandasamy[40]	2017, USA	No information	Prospective cohort, single center	Gestational age <32 wk	69/69	35	26 (3)	860 (375)	Unclear	Death or BPD according to NICHD definition and room air challenge

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Table I. Continued

First author	Year of publication, country	Period of data collection	Study design	Inclusion criteria	Number of participants eligible/analyzed	Number of outcome events	Gestational age, wk, mean (SD) or median [IQR]	Birth weight, g, mean ± SD or median [IQR]	Timing of model assessment	Defined outcome
Wai[37]	2016, USA	2010-2013	Randomized trial participants, multicenter (n = 25)	Gestational age <29 wk	511/474	336	25.2 (1.2)	700 (165)	D14	Death or BPD: respiratory support or oxygen supplementation at 36 weeks of PMA and room air challenge
El-Khuffash[36]	2015, Ireland, Canada, Australia	No information	Prospective cohort, multicenter (n = unknown)	Gestational age <29 wk	141/141	79	26.8 (1.4)	952 (235)	D2	Death or BPD: oxygen supplementation at 36 weeks of PMA
Kandasamy[35]	2015, USA	2005-2008	Prospective cohort, single center	BW < 1000 g	152/152	53	25.5 (2.8)	720.16 (147)	D1	Death or BPD according to NICHD definition and room air challenge
Popova[34]	2015, USA	No information	Prospective cohort, single center	Gestational age ≤32 wk	89/89	54	No BPD: 28.71 (2.58) BPD/death 25.93 (2.93)	No BPD: 1170 (490) BDP/death: 815 (266)	Unclear	Death or moderate/severe BPD: oxygen supplementation at 36 weeks of PMA.
Schneibel[32]	2013, USA	2006-2008	Prospective cohort, multicenter (n = 2)	Gestational age 23-31 wk; BW <1500 g	27/27	11	No/mild BPD 26.18 (1.86) Moderate/severe BPD 26.95 (2.63)	No/mild BPD 872 (245) Moderate/severe BPD 817 (263)	D1	Moderate/severe BPD: oxygen supplementation at 36 weeks of PMA.
Ambalavanan[30]	2011, USA	2001-2004	Randomized trial participants	BW 401-1250 g	2836/Unknown	1010	27.1 [25-29]	910 (206)	D7	Death or moderate/severe BPD: positive pressure support or FiO_2 >30% supplemental oxygen with SaO_2 90%-96% at 36 weeks of PMA and room air challenge.
Laughon[28]	2011, USA	2000-2004	Randomized trial participants, multicenter (n = 17)	Gestational age 23-29 wk; BW 401-1250 g	3636/3629	2411	26.7 (1.9)	897 (203)	D1, D3, D7 and D14	Death or mild/moderate/severe BPD according to NICHD definition.
Messerschmidt[27]	2011, Austria	1999-2007	Retrospective cohort, single center	BW ≤1500 g	300/223	33	No/mild BPD 27.3 (1.9) Moderate/severe BPD 25.9 (1.5)	No information	D1	Moderate/severe BPD: oxygen supplementation at 36 weeks of PMA.
Subramanian[26]	2011, USA	1994-1997	Retrospective cohort, multicenter (n = 9)	Gestational age <36 wk; BW 500-1499 g	493/425	74	28.9 (2.5)	1091 (260)	D6	Moderate/severe BPD: oxygen supplementation at 36 weeks of PMA.
Ambalavanan[25]	2008, USA	2001-2003	Randomized trial participants, multicenter (n = unclear)	Gestational age <34 wk; BW 401-1500 g	420/417	321	26 (2)	840 g (260)	Unclear	Death or BPD: room air challenge.

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Table I. Continued

First author	Year of publication, country	Period of data collection	Study design	Inclusion criteria	Number of participants eligible/analyzed	Number of outcome events	Gestational age, wk, mean (SD) or median [IQR]	Birth weight, g, mean ± SD or median [IQR]	Timing of model assessment	Defined outcome
Choi[23]	2006, Korea	1998-2002	Prospective cohort, single center	Gestational age ≤32 wk	75/75	45	No/mild BPD 29 (2.4) Moderate/severe BPD 27.7 (2)	No/mild BPD 1221 (361) Moderate/severe BPD 1010 (246)	Unclear	Moderate/severe BPD: >28 days oxygen supplementation and oxygen supplementation at 36 weeks of PMA and consistent chest radiograph findings.
Henderson-Smart[22]	2006, Australia and New-Zealand	1998-1999	Prospective cohort, multicenter (n = 25)	Gestational age 22-31 wk	5599/5599	1235	29 [27-30]	1235 [960-1505]	At birth	Moderate/severe BPD: oxygen supplementation or any form of assisted ventilation at 36 weeks of PMA.
Kim[21]	2005, Korea	1997-1999	Retrospective, single center	BW <1500 g	197/161	30	28.2 (1.9)	1043 (262.6)	D4, D7 and D10	Moderate or severe BPD: oxygen supplementation at 36 weeks of PMA.
Ng[19]	2004, China	No information	Prospective cohort, single center	Gestational age <32 wk; BW < 1500	137/101	45	No/mild BPD 26.4 [24.9-28.3] BPD/death 29.1 [27.8-30.6]	No/mild BPD 860 [706-1148] BPD/death 1168 [1034-1329]	D14	Death or BPD: oxygen supplementation at 36 weeks of PMA.
Chien[18]	2002, Canada	1996-1997	Unclear, multicenter (n = 17)	Gestational age ≤32 wk	4907/4226		29 (2)	1390 (457)	H12	Moderate/severe BPD: oxygen supplementation at 36 weeks of PMA.
Lui[17]	2000, Australia	1992-1995	Prospective cohort	BW < 1000	48/46	12	26 (1)	805 (102)	Unclear	Moderate/severe BPD: oxygen supplementation beyond 36 weeks of PMA.
Yoder[16]	1999, USA	1990-1992	Retrospective cohort, single center	Gestational age ≤29 wk; BW ≤1000 g	48/48	15	Unclear	Unclear	H12, H72	Death or BPD: oxygen supplementation at 36 weeks of PMA and abnormal chest radiograph. Death after D7 related to persistent severe pulmonary disease.
Subhedar[14]	1998, United Kingdom	1994-1996	Prospective cohort, single center	Gestational age <32 wk	55/55	26	28 [23-31]	920 [580-2256]	H24	Death or BPD: >28 days oxygen supplementation and oxygen supplementation beyond 36 weeks of PMA.
Ryan[13]	1996, United Kingdom	1991-1992	Retrospective cohort, single center	Gestational age <32 wk	204/Unknown	51	28 [23-31]	1160 [512-2300]	D4	Moderate/severe BPD: oxygen supplementation to achieve SaO_2 >92% at 36 weeks of PMA and abnormal chest radiograph.

(*continued*)

Table I. Continued

First author	Year of publication, country	Period of data collection	Study design	Inclusion criteria	Number of participants eligible/analyzed	Number of outcome events	Gestational age, wk, mean (SD) or median [IQR]	Birth weight, g, mean ± SD or median [IQR]	Timing of model assessment	Defined outcome
Validation studies										
Alonso-Ojembarrena[71]	2022, Spain	2017-2021	Case–control, multicenter (n = 2)	Gestational age <32 wk	199/133	27	no BPD group 30 [29-31] BPD group 27 [25-29]	no BPD 1300 [1100-1445]; BPD 905 (620-1000)	D1, D3, D7, D14	Moderate/severe BPD: any respiratory support at 36 weeks of PMA
Aldecoa-Bilbao[57]	2021, Spain	2018-2020	Prospective cohort single center	Gestational age $23^{0/7}$ to $30^{6/7}$ wk	152/89	23	28.1 [26.7-29.8]	BPD: 856 (284) No BPD: 1077 (320)	D7	Moderate/severe BPD: supplemental oxygen or positive pressure ventilation at 36 WG
Alonso-Ojembarrena[52]	2021, Spain	2017-2020	Prospective cohort, multicenter (n = 6)	Gestational age <32 wk	356/298	73	29 [26-30]	1100 [859-1340]	D0, D3, D7, D14	BPD at 36 WG - physiologic definition (Walsh test)
Baud[58]	2021, Europe, USA	2008-2014	Randomized trial participants, multicenter (n = 21)	Gestational age $24^{0/7}$ to $27^{6/7}$ wk	523/523	232	26.5 [25.7–27.1]	840 (735–970)	at birth	Death or moderate/severe BPD: respiratory support at 36 WG, physiologic test if FiO_2 22%-29%
Bhattacharjee[56]	2021, USA	2012-2013	Retrospective cohort, single center	ELBW	69/64	31	25 [21-28]	723 (160)	D3	Severe BPD: >30% O_2 and/or positive pressure ventilation or CPAP at 36 wk or discharge
Gerull[60]	2021, Switzerland	2013-2017	Prospective cohort, multicenter (n = 2)	Gestational age <32 wk	523/229	26	29.6 [27.0-30.7]	1150 [840-1410]	D7	Death/BPD at 36 weeks
Liu[62]	2021, China	2019-2020	Prospective cohort, single center	Gestational age <32 wk	130/130	50	29.2 (1.8)	1195 (2&à)	D1, D2, D3, D6, D9, D12	BPD: 2019 definition by Jensen
Mohamed[63]	2021, Canada	2019-2020	Prospective cohort, multicenter (n = 2)	Gestational age <29 wk	223/152	87	25.8 (1.5)	923 (250)	D3, D7, D14	BPD: supplementation of oxygen or respiratory support at 36 WG
Shim[64]	2021, South Korea	2013-2016	Registry data, multicenter (n = 66)	Unclear	6969/1795	1370	BPD 0 30.61 (1.80); BPD 1 27.49 (1.84); BPD 2 27.37 (2.18); BPD 3 26.64 (2.34)	BPD 0 127 (174); BPD 1 1058 (23′); BPD 2 1025 (24); BPD 3 886 (264)	D0	Moderate and severe BPD: NIH definition
Ushida[67]	2021, Japan	2006-2015	Registry data, multicenter (n = 200)	Gestational age <32 wk; BW < 1500g	33 690/20 771	4986	27.8 (2.5)	975 (299)	D0	BPD: oxygen requirement at 36 wk
Woods[68]	2021, Australia	2017-2018	Prospective cohort, single center	Gestational age <28 wk	125/96	46	26.4 (range 23.1-27.6)	855 (range 450-1390)	D1, D3, D7	moderate/severe BPD: respiratory support at 36 wk

(*continued*)

Table I. Continued

First author	Year of publication, country	Period of data collection	Study design	Inclusion criteria	Number of participants eligible/analyzed	Number of outcome events	Gestational age, wk, mean (SD) or median [IQR]	Birth weight, g, mean ± SD or median [IQR]	Timing of model assessment	Defined outcome
Bhattacharjee[56]	2020, USA	2012-2013	Retrospective cohort, single center	BW < 1000 g	69/64	31	25 [21-28]	722 (160)	Unclear	Severe BPD: >30% supplemental oxygen and/or positive pressure ventilation or nasal CPAP at 36 weeks of PMA or at time of discharge.
Oulego-Erroz[55]	2020, Spain	2017-2019	Prospective cohort, single center	Gestational age <32 wk	42/42	13	No/mild BPD 29.5 [28-31.5] BPD/death 27 [25.7-28.2]	No/mild BPD 1235g [1110–1507] BPD/death 890 g [655–1130]	D7	Moderate/severe BPD: oxygen supplementation or positive pressure ventilation at 36 weeks of PMA.
Sotodate[53]	2020, Japan	2010-2017	Retrospective cohort, single center	Gestational age 22-27 wk	171/152	69	25.7 (1.5)	768 (201)	H1, H12, and D1 after NICU admission	Moderate/severe BPD: oxygen supplementation or positive pressure ventilation at 36 weeks of PMA.
Alonso-Ojembarrena[52]	2019, Spain	2017-2018	Prospective cohort, single center	Gestational age ≤32 wk or BW ≤1500 g	64/59	8	No BPD 29.5 (95% CI 27-32) Mild/moderate/severe BPD 27.4 (95% CI 23-31)	No BPD 1241(95% CI 837-1440 g) Mild/moderate/severe BPD 914 (95% CI 461-1367)	D1, D3, D7 and D14	Moderate/severe BPD: >28 days oxygen supplementation and oxygen supplementation or respiratory support at 36 weeks of PMA and room air challenge.
Beltempo[50]	2019, Canada	2010-2015	Retrospective cohort, multicenter (n = 30)	Gestational age $22\text{-}28^{6/7}$ wk	9240/7975	2959	27 [3-unclear]	953 (244)	H12 after NICU admission	BPD: oxygen supplementation at 36 weeks of PMA or at time of discharge.
Jung[48]	2019, South Korea	2010-2014	Retrospective cohort, single center	Gestational age <28 wk	140/138	66	No/mild/moderate BPD 26.2 (1.2); death/severe BPD 25.5 (1.4)	No/mild/moderate BPD 822.36 g (226.6); death/severe BPD 733.79 (214.42)	D7	Death or severe BPD: FiO_2 >0.3 or positive pressure ventilation at 36 weeks of PMA.
Lee[47]	2019, South Korea	2013-2016	Prospective cohort, multicenter (n = 67)	Gestational age 22-32 wk; VLBW	Group 1 7198/4649 Group 2 7198/6038	Group 1 1443 Group 2 1916	Group 1 28.4 (2.4) Group 2 28.3 (2.4)	Group 1 1070.8 (280.4) Group 2 1058.5 (282.5)	H1	Moderate/severe BPD according to NICHD definition.
Gulliver[42]	2018, USA	2010-2016	Prospective cohort, single center	Gestational age <30 wk	622/Unknown	284	27.0 (1.9)	963 (301)	D7 and D14	Death or BPD: >28 days oxygen supplementation and beyond 36 weeks of PMA with modified criteria accounting for altitude.
Özcan[39]	2017, Turkey	2011-2012	Retrospective cohort, single center	Gestational age 24-31 wk; BW 400-1499 g	246/246	28	29.2 (2.15)	1323 (331.4)	H12	Moderate/severe BPD: oxygen supplementation at 36 weeks of PMA.

(*continued*)

Table I. Continued

First author	Year of publication, country	Period of data collection	Study design	Inclusion criteria	Number of participants eligible/analyzed	Number of outcome events	Gestational age, wk, mean (SD) or median [IQR]	Birth weight, g, mean ± SD or median [IQR]	Timing of model assessment	Defined outcome
Sullivan[38]	2016, USA	2004-2014	Retrospective cohort, single center	BW <1500 g	566/503	98	28.6 (2.9)	No information	H12, D1, D7	Moderate/severe BPD: oxygen supplementation at 36 weeks of PMA.
Truog[33]	2014, USA	2008-2010	Retrospective cohort, single center	Gestational age <29 wk	158/147	37	No information	No information	D7 and D14	Death or severe BPD: FiO_2 >0.3 or positive pressure ventilation to maintain SpO2>90% at 36 weeks of PMA or at time of discharge.
Sehgal[31]	2013, Australia	2010-2012	Retrospective cohort, single center	Gestational age <32 wk	52/52	27	26 [25-27]	788.5 [665.5-941]	Unclear	Moderate/severe BPD: oxygen supplementation or respiratory support at 36 weeks of PMA.
Ambalavanan[30]	2011, USA	2006	Prospective cohort, multicenter (n = 14)	BW 401-1250 g	2794/Unknown	1458	26.7 [25-29]	874 (230)	D7	Death or moderate/severe BPD: positive pressure support or FiO_2 >30% supplemental oxygen with SaO_2 90%-96% at 36 weeks of PMA and room air challenge.
Carvalho[29]	2011, Brazil	2002-2009	Prospective cohort, multicenter (n = 2)	Gestational age 24-33 wk	86/86	20	28.0 [24-33]	772 [360-1498]	H12	Moderate/severe BPD: oxygen supplementation at 36 weeks of PMA.
Laughon[28]	2011, USA	2000-2004	Randomized trial participants, multicenter (n = unclear)	24-$27^{6/7}$ wk	Group 1 1055/ Unknown Group 2 722/Unknown	Group 1 854 Group 2 571	Group 1 25.7 (1.1) Group 2 25.7 (1.1)	Group 1 830 (175) Group 2 842 (168)	D1, D3, D7 and D14	Death or mild/moderate/severe BPD according to NICHD definition.
May[24]	2007, United Kingdom	Group 1 1995-1998 Group 2 2004-2005	Group 1, randomized trial participants; group 2, prospective cohort	Group 1, gestational age <33 wk; BW <1500 g; group 2, gestational age <33 wk	Group 1 136/131 Group 2 75/75	Group 1 38 Group 2 22	Group 1 28 [23-33] Group 2 30 [23-32]	Group 1 1979 [592-1494] Group 2 1246 [555-2164]	D2, D7	Moderate/severe BPD: oxygen supplementation at 36 weeks of PMA.
Henderson-Smart[22]	2006, Australia and New-Zealand	2000-2001	Prospective cohort, multicenter (n = 25)	Gestational age 22-31 wk	5854/5854	1425	29 [27-30]	1235 [960-1510]	At birth	Moderate/severe BPD: oxygen supplementation or any form of assisted ventilation at 36 weeks of PMA.
Kim[21]	2005, Korea	2000-2001	Prospective cohort	BW <1500 g	107/96	9	28.5 (1.9)	1095 (270)	D4, D7, D10	Moderate or severe BPD: oxygen supplementation at 36 weeks of PMA.

(*continued*)

Table I. Continued

First author	Year of publication, country	Period of data collection	Study design	Inclusion criteria	Number of participants eligible/analyzed	Number of outcome events	Gestational age, wk, mean (SD) or median [IQR]	Birth weight, g, mean ± SD or median [IQR]	Timing of model assessment	Defined outcome
Greenough[20]	2004, United Kingdom	Group 1 1998-2001 Group 2 1995-1998	Randomized trial participants, single center	Group 1, gestational age 23-28 wk Group 2, BW ≤1500	Group 1 59/48 Group 2 40/32	Group 1 39 Group 2 18	Group 1 26 [24-28.6] Group 2 27 [25-31]	Group 1 768 [528-1097] Group 2 820 [590-1450]	D7	Moderate/severe BPD: oxygen supplementation at 36 weeks of PMA.
Chien[18]	2002, Canada	1996-1997	Unclear, multicenter (n = 17)	Gestational age ≤32 wk	4907/4226	Unknown	29 (2)	1390 (457)	H12	Moderate/severe BPD: oxygen supplementation at 36 weeks of PMA.
Yoder[16]	1999, USA	1993-1995	Group 1 prospective cohort, single center Group 2 retrospective cohort, multicenter (n = 2)	Gestational age ≤29 wk; BW ≤1000 g	Group 1 54/54 Group 2 56/56 Group 3 158/158	Group 1 14 Group 2 19 Group 3 48	Group 1 27 (2) Group 2 26 (2) Group 3 unknown	Group 1 919 (217) Group 2 892 (228) Group 3 unknown	H12, H72	Death or BPD: oxygen supplementation at 36 weeks of PMA and abnormal chest radiograph. Death after D7 related to persistent severe pulmonary disease.
Hentschel[15]	1998, Germany	1991-1993	Retrospective cohort, single center	BW <1500 g	Group 1 195/156 Group 2 195/168 Group 3 195/152 Group 4 195/157 Group 5 195/164 Group 6 195/179 Group 7 195/104 Group 8 195/119	Group 1 unknown Group 2 72 Group 3 unknown Group 4 72 Group 5 Unknown Group 6 72 Group 7 unknown Group 8 72	28.57 (2) [23.0-35.0]	1101 (281) [440-1495]	At admission, H12, D10	4 models with outcome moderate/severe BPD: oxygen supplementation at 36 weeks of PMA. 4 models with outcome death/BPD: oxygen supplementation at 36 weeks of PMA.
Subhedar[14]	1998, United Kingdom	1994-1996	Prospective cohort, single center (same center)	Gestational age <32 wk	28/28	23	29 [24-31]	1044 [520-1720]	H24	Death or BPD: >28 days oxygen supplementation and oxygen supplementation beyond 36 weeks of PMA.
Ryan[13]	1996, United Kingdom	1993	Retrospective cohort, single center (same center)	Gestational age <32 wk	47/Unknown	Unknown	Unknown	Unknown	D4	Moderate/severe BPD: oxygen supplementation to achieve SaO_2 >92% at 36 weeks of PMA and abnormal chest radiograph.

BPD, bronchopulmonary dysplasia; *BW*, birth weight; *CPAP*, continuous positive airway pressure; *ELBW*, extremely low birth weight; *FiO_2*, fraction of inspired oxygen; *NICHD*, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development; *NICU*, neonatal intensive care unit; *NIH*, National Institutes of Health; *PMA*, postmenstrual age; *SaO_2*, arterial oxygen saturation; *WG*, weeks of gestation.

Table II. Characteristics of the included models

Characteristics	Developed models, n = 158*		Validated models, n = 108*	
Participants and predictors	**No. (%)**	**Median [min-max]**	**No. (%)**	**Median [min-max]**
Total sample size—eligible	157 (99.4)	778 [27-156 587]	107 (99.1)	158 [28-9240]
Total sample size—analyzed	141 (89.2)	474 [22-20 771]	94 (87.0)	130 [28-7975]
Number of outcome events	155 (98.1)	232 [11-6121]	100 (92.6)	50 [8-2959]
Number of candidate predictors	150 (94.9)	15 [1-50]	NA	NA
Events per predictor for model development	149 (94.3)	102.9 [0.33-986.3]	NA	NA
Number of predictors in the final model	158 (100.0)	6 [2-21]	NA	NA
Type of predictors in final model	**No. (%)**		**No. (%)**	
Routinely collected data only†	111 (70.3)		59 (37.3)	
Echocardiographic data	4 (2.5)		2 (1.9)	
Lung mechanics/imaging	20 (12.7)		47 (43.5)	
Blood biomarkers	11 (7.0)		0 (0.0)	
Tracheal biomarkers	3 (1.9)		0 (0.0)	
Urinary biomarkers	2 (1.3)		0 (0.0)	
Genetic biomarkers	2 (1.3)		0 (0.0)	
Combination of above	5 (3.2)		0 (0.0)	
Timing of model assessment	**No. (%)**		**No. (%)**	
At birth	7 (4.4)		5 (1.5)	
At admission	1 (0.6)		2 (1.9)	
1 hour after admission	0 (0.0)		3 (2.8)	
12 hours after admission	6 (3.8)		15 (13.9)	
Day 1	28 (17.7)		13 (12.0)	
Day 2	2 (1.3)		5 (4.6)	
Day 3	15 (9.5)		15 (13.9)	
Day 4	2 (1.3)		3 (2.8)	
Day 6	4 (2.5)		3 (2.8)	
Day 7	49 (31.0)		23 (21.3)	
Day 9	3 (1.9)		3 (2.8)	
Day 10	2 (1.3)		4 (3.7)	
Day 12	0 (0.0)		3 (2.8)	
Day 14	28 (17.7)		9 (8.3)	
Unclear	11 (7.0)		2 (1.9)	
Methodologic aspects of model development	**No. (%)**			
Handling of missing data				
Complete-case analysis	55 (34.8)			
Single/multiple imputation	52 (32.9)			
Unclear or no information	51 (32.3)			
Handling of linear predictors				
Appropriately	19 (12.0)			
Not appropriately	12 (7.6)			
No information	100 (63.3)			
Modeling method				
Logistic regression	110 (69.6)			
CART analysis	5 (3.2)			
Other	97 (61.4)			
Selection of predictors in multivariable model				
Preselection based on univariable analysis	40 (25.3)			
All candidate predictors	89 (56.3)			
Exclusion of variables from previous model	1 (0.6)			
Addition of variables to previous model	3 (1.9)			
LASSO	1 (0.6)			
Best goodness-of-fit parameters	2 (1.3)			
Unclear	22 (13.9)			
Selection of predictors in final model				
All predictors forced in model	72 (45.6)			
All candidate predictors	3 (1.9)			
Backwards stepwise selection	17 (10.8)			
Forwards stepwise selection	21 (13.3)			
Both FW and BW stepwise selection	9 (5.7)			
Stepwise selection	8 (5.1)			
Same variables used as in stepwise logistic regression model	1 (0.6)			
All possible combinations	1 (0.6)			
Best performance of model	1 (0.6)			
LASSO	2 (1.3)			
Tree pruning	1 (0.6)			
Chosen by authors	2 (1.3)			
Unclear	20 (12.7)			
Internal validation	78 (49.4)			
Method of validation				
Random split of data	15 (9.5)			

(*continued*)

Table II. Continued

Characteristics	Developed models, n = 158*		Validated models, n = 108*	
Cross-validation	56 (35.4)			
Resampling of same data set	7 (4.4)			
Unclear	3 (1.9)			
External validation in same paper	16 (10.1)			
Model presentation				
Final full model presented, including intercept	17 (10.8)			
Online tool	5 (3.2)			
Probability chart	1 (0.6)			
Sum score	5 (3.2)			
Nomograms	2 (1.3)			
Discrimination and calibration of model performances	**No. (%)**	**Median [min-max]**	**No. (%)**	**Median [min-max]**
Discrimination				
C-statistic, apparent	145 (91.8)	0.84 [0.43-1.00]	105 (97.2)	0.77 [0.41-0.97]
C-statistic after internal validation	74 (46.8)	0.86 [0.67-0.91]		
Calibration apparent				
Hosmer-Lemeshow, No. (%)	13 (7.5)		3 (2.8)	
Calibration plot, No. (%)	4 (2.5)		0 (0.0)	
Predicted and observed probabilities, No. (%)	48 (30.4)		2 (1.9)	

BW, backward; *CART*, Classification and Regression Tree; *FW*, forward; *LASSO*, least absolute shrinkage and selection operator; *NA*, not available.
*The 158 developed models include 141 developed only models and 17 developed models with external validation. The 108 validated models include 87 only validated models and 21 developed models with external validation.
†Routinely collected data including sociodemographic characteristics, pregnancy and neonatal events, and standard laboratory finding.

of 0.84 (range 0.43-1.00) (Table II). C-statistics after internal validation were reported in most models (94.9%) with a median c-statistic of 0.86 (range 0.67-0.91). Calibration was reported in 13 models (7.5%) with Hosmer–Lemeshow tests,[18,22,26] and 4 models (2.5%) showed a calibration plot.

Seventeen models (10.8%) were reported fully, including the intercept and all the final predictor weights from logistic regression modeling or the final classification tree from Classification and Regression Tree analysis. Two studies developed an online prediction tool that provides individual prediction of death/BPD risk at day 1, 3, 7, and 14 of life.[28,72]

Predictors in the Final Developed Models. Mostofthepredictionmodels (70.3%) included routinely collected data (Table II). Among those, gestational age, birth weight, sex, and information about early respiratory status were most often included (Figure 2). Other frequently used predictors were blood biomarkers,[19,35,40,51] tracheal samples,[23,32,34] lung mechanics/imaging,[17,45,52,57,62,63,68,71] and echocardiographic data.[14,36,51,74] Finally, a few models included illness severity scores,[19,26,51] urinary biomarkers,[70] genetic biomarkers,[59] and vitalorventilatorparameters.[41,49]

External Validation of BPD Prediction Models

The total number of analyzed infants was reported for most of the externally validated models (87.0%) as well as the number of infants with the outcome (92.6%) (Table II). Most of the models (81%) were validated in data that included fewer than 100 outcome events. Fifty-five models (50.9%) were validated with complete-case analysis, and 5 (4.6%) reported no missing data. Validated models were mainly assessed at day 7 after birth (21.3%), at day 3 (13.9%) or up to 12 hours after admission (13.9%), using mostly predictors from lung mechanics/imaging (43.5%) or routinely collected data (37.3%) (Table II). Fifteen studies performed external validation of existing prediction models, illness severity scores.[15,18,28,29,33,38,39,42,47,48,50,53,56,60]

Predictive Performances of Externally Validated Models. C-statistics were reported in almost all models (97.2%) with a median c-statistic of 0.77 (range 0.41-0.97). Calibration was reported in 3 models (2.8%) with Hosmer–Lemeshow tests[18,22,29] or a table of predicted and observed probabilities (1.9%).[42]

In the 7 studies that reported both the development and external validation,[13,16,21,22,28,30,67] discrimination were very similar between model development and validation (median c-statistic 0.83 [range 0.76-0.96] and 0.84 [range 0.70-0.97]), respectively. The Hosmer–Lemeshow test was used in one study.[22]

In total, 57 externally validated models predicting BPD were included in the meta-analysis and the pooled c-statistic was 0.78 (95% CI 0.74-0.82, 95% PI 0.48-0.93) (Figure 3, A) and increased after the first week of life, but with overlapping CIs at the different time points (Figure 4). Finally, the pooled c-statistic from the 21 externally validated models predicting death/BPD was 0.82 (95% CI 0.79-0.85, 95% PI 0.66-0.92) (Figure 3, B) and was quite similar at the different time points (Figure 4).

RoB and Applicability Assessment

All developed models were rated at high RoB in the analysis domain (Figure 5). This was due to issues with small sample size (events per variable <10), inadequate handling of missing data by omitting participant with missing data from the analysis, and subsequently using complete case analysis instead of using multiple imputation, selection of predictors based on univariable analysis before multivariable modeling, competing risk by death not accounted for, and absence of internal validation as part of

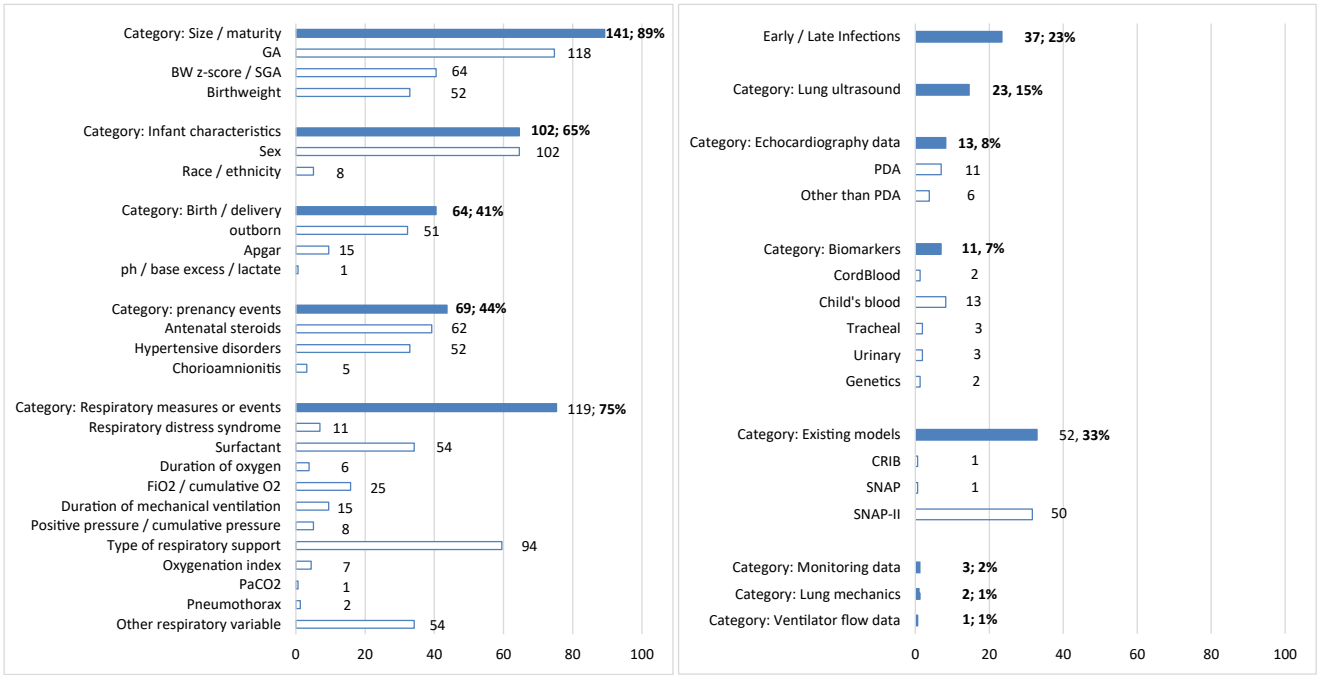

Figure 2. Frequency of variables used in the development models. *Labels* indicate the number of occurrences of each variable out of the 158 models. The *categories* indicate how often one of the predictors mentioned below were included in one of the development models.

model development. In addition, most studies only reported a c-statistic as performance measure of model performances; however, calibration was mostly not or inadequately reported (eg, reporting Hosmer–Lemeshow instead of calibration plot). These items resulted in a high RoB rate for the analysis domain for all developed models. Most of the models scored a low RoB in the participants and predictor domains. In one study, the eligible population could not be determined at the time of model assessment at day 7, because one of the inclusion criteria was ventilation during the first four weeks of life.[48] Inclusion or exclusion criteria were unclear in 3 studies.[30,34,70] Four studies considered predictors[19,23,26,59] that were not available at the time of BPD risk assessment. Others did not assess predictors at the same time for all infants[34,54] or gave unclear definitions for predictors.[13,57] Some models also scored high (11.3%) or unclear (5.7%) RoB on the outcome domain, mainly due to BPD assessment occurring earlier than 36 weeks in infants transferred or discharged before 36 weeks of PMA (**Table I**). Because all models scored high RoB in one of the domains, the overall RoB was rated as high.

Most of the models had low concern on overall applicability. Concerns on applicability were often due to highly selected populations, when only infants with mechanical ventilation or with severe respiratory disease were included. Some studies considered radiographic results to define BPD,[13,16,23] which is not recommended anymore. A complete overview of the RoB and applicability assessment per model is shown in **Table III**).

Model Validation. All validated models but one were rated at high RoB in the analysis domain (**Figure 5**), mostly due to a small sample size (<100 outcome events). In 2 studies, external validation was performed on 9 and 28 events, respectively.[14,21] Other issues were inadequate handling of missing data, competing risk by death not accounted for, and lack of assessment of calibration. Most of the validated models scored low RoB for participants, predictor, and outcome domains; however, because all models but one scored high RoB in the analysis domain, the overall RoB was rated as high. Most models had also low concerns on applicability (**Figure 5**, **Table III**).

Discussion

This systematic review identified 65 studies that developed or validated a multivariable prediction model for BPD or death/BPD at 36 weeks of PMA during the 14 first days of life. In total, 158 development and 108 validated models were reviewed. These models included mainly routinely collected data, such as clinical information and routine laboratory findings.

Although discrimination was satisfactory with a median c-statistic of 0.84 in the development models, and 0.77 in the validated models, these results must be interpreted with

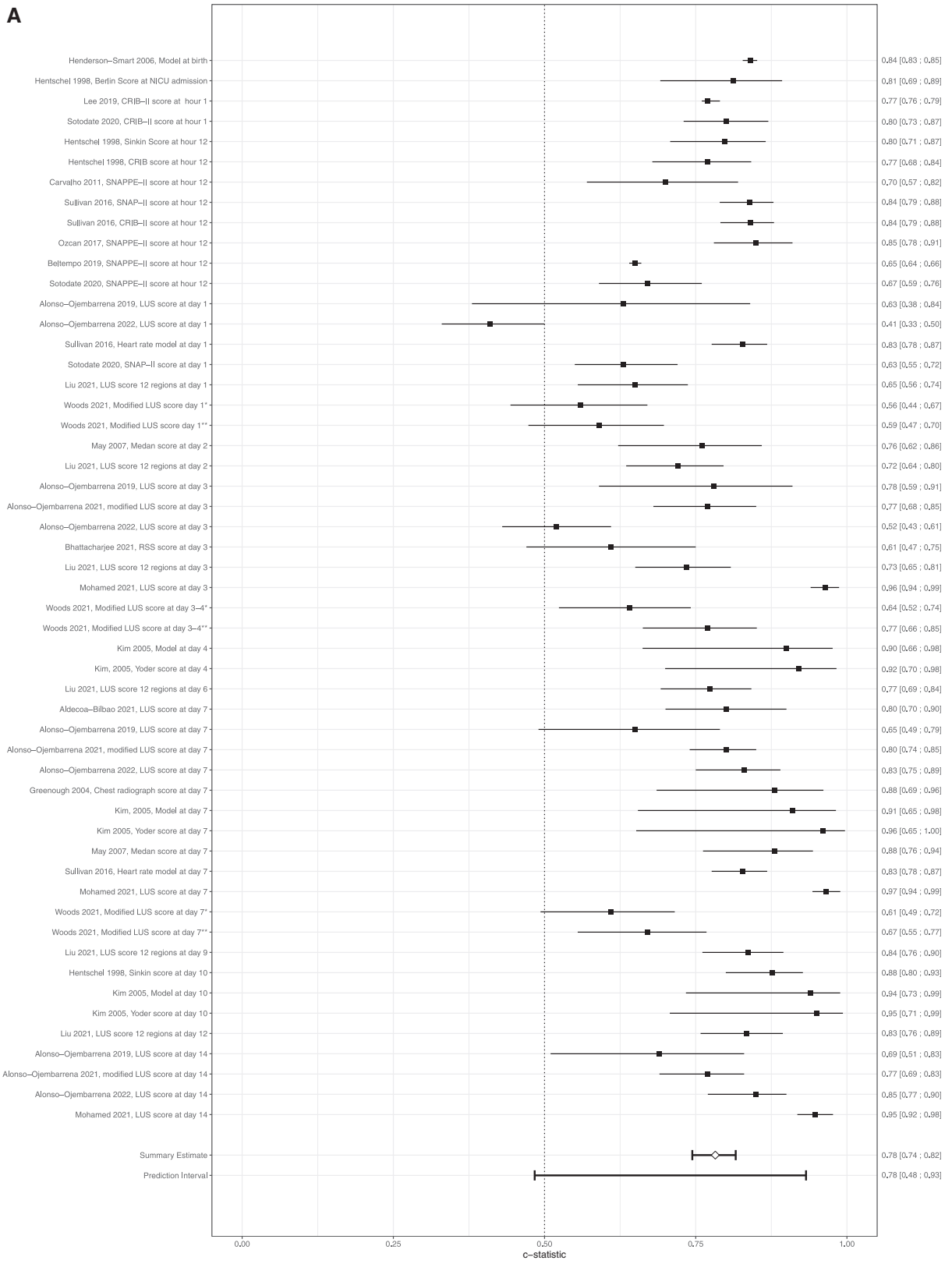

Figure 3. Meta-analysis of externally validated models predicting **A,** BPD or **B,** death/BPD at 36 weeks of PMA. *Prediction model externally validated on outcome moderate or severe BPD. **Prediction model externally validated on outcome grade II or III BPD. *(Continues)*

Figure 3. Continued.

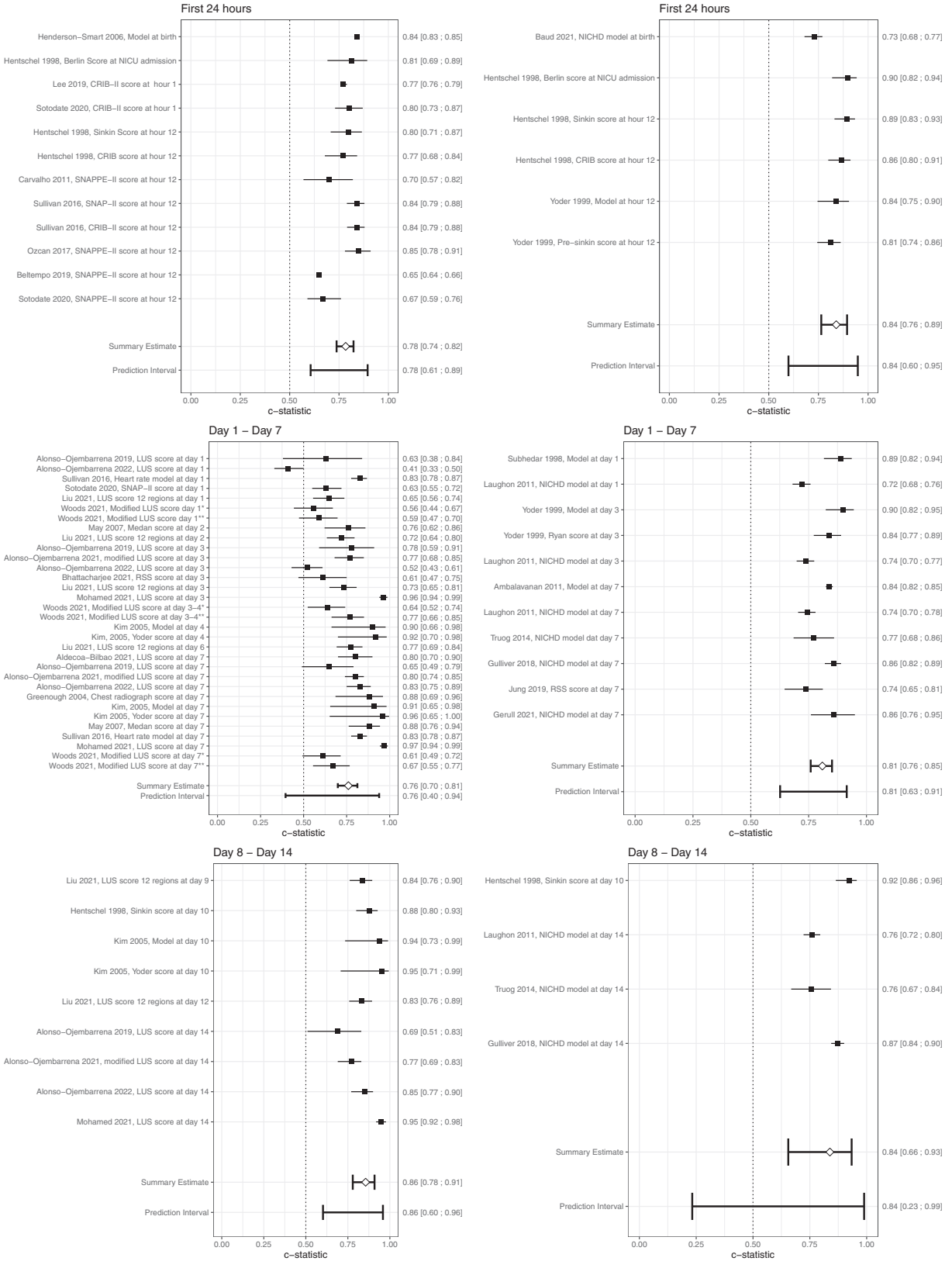

Figure 4. Meta-analysis of externally validated models by timing assessment, predicting BPD (*left*) and death/BPD (*right*). *Prediction model externally validated on outcome moderate or severe BPD. **Prediction model externally validated on outcome grade II or III BPD.

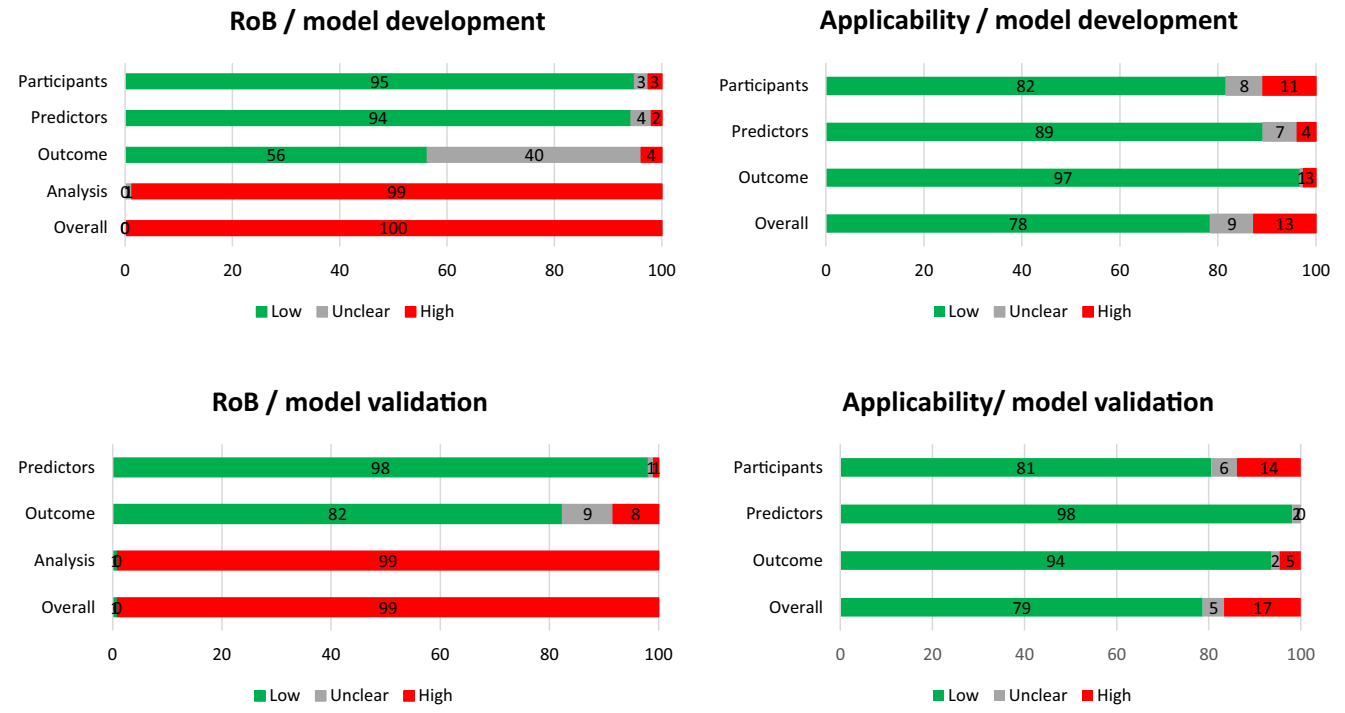

Figure 5. RoB and applicability assessment for the 158 development and the 108 externally validated model.

caution as all models scored high for RoB or had applicability concerns. The main bias issues were found in the analysis domain of the PROBAST guidelines, with small sample sizes, inappropriate handling of missing data, absence of internal or external validation, and inappropriate report or absence of calibration measures. Applicability issues were mainly due to highly selected populations that were particularly at risk of developing BPD.

In 2013, a systematic review included clinical BPD prediction models published up to 2011.[6] In contrast with that review, the current review only included studies that defined BPD at 36 weeks of PMA, because this time point has an improved association with long term respiratory and neurological outcomes than the 28 days definition.[76,77] Although most studies used the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development 2001 definition (80%), variability in the BPD definitions used throughout the studies might have contributed to some variability in the c-statistics. A second difference with the 2013 review and a strength of the current review is that all models were assessed with a formal RoB assessment tool, PROBAST.[8] We noted that all studies had a high RoB, and most studies had a high RoB in the analysis domain. One of the main general flaws in this domain of all existing prediction models is that calibration was rarely assessed or reported. Only 4 studies reported the results of the Hosmer–Lemeshow goodness-of-fit test,[18,22,26,29] which has been recognized as inadequate, as it is influenced by sample size and gives no indication of direction or magnitude of miscalibration.[78] A calibration plot is the preferred method to report calibration performance of a prediction model; this finding was also highlighted in the recent systematic review about mortality prediction models in infants born preterm.[79] Assessing the accuracy of absolute risk estimates is a key element that provides useful information for clinical decision-making and should be evaluated before considering using a prediction model in clinical practice.[80] Another main flaw in this domain that caused high RoB was the small sample size, with events per variable <10, which increases the risk of overfitting for which correction with internal validation is necessary. Most models did not perform internal validation or performed an inadequate method using random split of data. Only a few models used cross-validation, which is, next to bootstrapping, recommended to account for overfitting and optimism in a developed prediction model. Finally, most models scored high RoB in the analysis domain due to inappropriate or unclear handling of missing data. Some studies excluded those participants with missing data and performed complete case analysis, which leads to biased model performances. Instead, multiple imputation is recommended to reduce the risk of bias.

Research in BPD prediction has shifted toward the identification of early biomarkers or imaging tools. Many reports of univariate associations between biomarkers and BPD have shown promising data.[81,82] Very few multivariable models using blood, tracheal biomarkers, or lung ultrasound

Table III. Risk of bias and applicability assessment for A, each development model and B, for each validated model

Study	Year	Model description (outcome, timing, type of predictors)	RoB				Applicability			Overall	
			Participants	Predictors	Outcome	Analysis	Participants	Predictors	Outcome	RoB	Applicability
Developmental models											
Ahmed[70]	2022	BPD, <H72, urinary biomarkers	?	+	+	-	+	+	+	-	+
		BPD, <H72, urinary biomarkers	?	+	+	-	+	+	+	-	+
Alonso-Ojembarrena[71]	2022	BPD, D1, LUS score + blood biomarkers	+	+	+	-	+	+	+	-	+
		BPD, D3, LUS score + blood biomarkers	+	+	+	-	+	+	+	-	+
		BPD, D7, LUS score + blood biomarkers	+	+	+	-	+	+	+	-	+
		BPD, D14, LUS score + blood biomarkers	+	+	+	-	+	+	+	-	+
		BPD, D7, clinical data	+	+	+	-	+	+	+	-	+
		BPD, D7, LUS score + clinical data	+	+	+	-	+	+	+	-	+
		BPD, D7, LUS score + blood biomarkers + clinical data	+	+	+	-	+	+	+	-	+
		BPD, D7, LUS score + blood biomarkers + clinical data	+	+	+	-	+	+	+	-	+
Greenberg[72]	2022	Death/BPD, D1, clinical data	+	+	?	-	+	+	+	-	+
		Death/BPD, D3, clinical data	+	+	?	-	+	+	+	-	+
		Death/BPD, D7, clinical data	+	+	?	-	+	+	+	-	+
		Death/BPD, D14, clinical data	+	+	?	-	+	+	+	-	+
Kindt[73]	2022	BPD, <D7, blood biomarkers	+	+	?	-	+	+	+	-	+
Umapathi[74]	2022	BPD, <D7, echocardiographic data	+	+	+	-	+	+	+	-	+
Zayat[75]	2022	BPD, D14, clinical data	+	+	+	-	+	+	+	-	+
Aldecoa-Bilbao[57]	2021	BPD, D7, LUS score + clinical data	+	+	+	-	+	+	+	-	+
Alonso-Ojembarrena[52]	2021	BPD, at admission, clinical data	+	+	+	-	+	+	+	-	+
		BPD, D3, clinical data	+	+	+	-	+	+	+	-	+
		BPD, D3, LUS score + clinical data	+	+	+	-	+	+	+	-	+

(*continued*)

Table III. Continued

Study	Year	Model description (outcome, timing, type of predictors)	RoB				Applicability			Overall	
			Participants	Predictors	Outcome	Analysis	Participants	Predictors	Outcome	RoB	Applicability
		BPD, D3, LUS score + clinical data	+	+	+	-	+	+	+	-	+
		BPD, D7, clinical data	+	+	+	-	+	+	+	-	+
		BPD, D7, LUS score + clinical data	+	+	+	-	+	+	+	-	+
		BPD, D7, LUS score + clinical data	+	+	+	-	+	+	+	-	+
Baud[58]	2021	Death/BPD, at birth, clinical data	+	+	+	-	+	+	+	-	+
		Death/BPD, at birth, clinical data	+	+	+	-	+	+	+	-	+
Dai[59]	2021	Death/BPD, unclear, genetics + clinical data	+	?	+	-	?	+	+	-	?
		Death/BPD, unclear, clinical data	+	?	+	-	?	+	+	-	?
		Death/BPD, unclear, genetics + clinical data	+	?	+	-	?	+	+	-	?
Gerull[60]	2021	Death/BPD, D7, blood biomarkers + clinical data	+	+	+	-	+	+	+	-	+
		Death/BPD, D7, blood biomarkers + clinical data	+	+	+	-	+	+	+	-	+
		Death/BPD, D7, blood biomarkers + clinical data	+	+	+	-	+	+	+	-	+
Khurshid[61]	2021	Death/BPD, D1, clinical data	+	+	?	-	+	+	+	-	+
		Death/BPD, D1, clinical data	+	+	?	-	+	+	+	-	+
		Death/BPD, D1, clinical data	+	+	?	-	+	+	+	-	+
		Death/BPD, D1, clinical data	+	+	?	-	+	+	+	-	+
		Death/BPD, D1, clinical data	+	+	?	-	+	+	+	-	+
		Death/BPD, D1, clinical data	+	+	?	-	+	+	+	-	+
		Death/BPD, D1, clinical data	+	+	?	-	+	+	+	-	+
		Death/BPD, D1, clinical data	+	+	?	-	+	+	+	-	+
		Death/BPD, D7, clinical data	+	+	?	-	+	+	+	-	+
		Death/BPD, D7, clinical data	+	+	?	-	+	+	+	-	+

(*continued*)

Table III. Continued

Study	Year	Model description (outcome, timing, type of predictors)	RoB: Participants	RoB: Predictors	RoB: Outcome	RoB: Analysis	Applicability: Participants	Applicability: Predictors	Applicability: Outcome	Overall: RoB	Overall: Applicability
		Death/BPD, D7, clinical data	+	+	?	-	+	+	+	-	+
		Death/BPD, D7, clinical data	+	+	?	-	+	+	+	-	+
		Death/BPD, D7, clinical data	+	+	?	-	+	+	+	-	+
		Death/BPD, D7, clinical data	+	+	?	-	+	+	+	-	+
		Death/BPD, D7, clinical data	+	+	?	-	+	+	+	-	+
		Death/BPD, D7, clinical data	+	+	?	-	+	+	+	-	+
		Death/BPD, D14, clinical data	+	+	?	-	+	+	+	-	+
		Death/BPD, D14, clinical data	+	+	?	-	+	+	+	-	+
		Death/BPD, D14, clinical data	+	+	?	-	+	+	+	-	+
		Death/BPD, D14, clinical data	+	+	?	-	+	+	+	-	+
		Death/BPD, D14, clinical data	+	+	?	-	+	+	+	-	+
		Death/BPD, D14, clinical data	+	+	?	-	+	+	+	-	+
		Death/BPD, D14, clinical data	+	+	?	-	+	+	+	-	+
		Death/BPD, D14, clinical data	+	+	?	-	+	+	+	-	+
		Death/BPD, D1, clinical data	+	+	?	-	+	+	+	-	+
		Death/BPD, D1, clinical data	+	+	?	-	+	+	+	-	+
		Death/BPD, D1, clinical data	+	+	?	-	+	+	+	-	+
		Death/BPD, D1, clinical data	+	+	?	-	+	+	+	-	+
		Death/BPD, D1, clinical data	+	+	?	-	+	+	+	-	+
		Death/BPD, D1, clinical data	+	+	?	-	+	+	+	-	+
		Death/BPD, D1, clinical data	+	+	?	-	+	+	+	-	+
		Death/BPD, D1, clinical data	+	+	?	-	+	+	+	-	+

(continued)

Table III. Continued

Study	Year	Model description (outcome, timing, type of predictors)	RoB				Applicability			Overall	
			Participants	Predictors	Outcome	Analysis	Participants	Predictors	Outcome	RoB	Applicability
		Death/BPD, D7, clinical data	+	+	?	-	+	+	+	-	+
		Death/BPD, D7, clinical data	+	+	?	-	+	+	+	-	+
		Death/BPD, D7, clinical data	+	+	?	-	+	+	+	-	+
		Death/BPD, D7, clinical data	+	+	?	-	+	+	+	-	+
		Death/BPD, D7, clinical data	+	+	?	-	+	+	+	-	+
		Death/BPD, D7, clinical data	+	+	?	-	+	+	+	-	+
		Death/BPD, D7, clinical data	+	+	?	-	+	+	+	-	+
		Death/BPD, D7, clinical data	+	+	?	-	+	+	+	-	+
		Death/BPD, D14, clinical data	+	+	?	-	+	+	+	-	+
		Death/BPD, D14, clinical data	+	+	?	-	+	+	+	-	+
		Death/BPD, D14, clinical data	+	+	?	-	+	+	+	-	+
		Death/BPD, D14, clinical data	+	+	?	-	+	+	+	-	+
		Death/BPD, D14, clinical data	+	+	?	-	+	+	+	-	+
		Death/BPD, D14, clinical data	+	+	?	-	+	+	+	-	+
		Death/BPD, D14, clinical data	+	+	?	-	+	+	+	-	+
		Death/BPD, D14, clinical data	+	+	?	-	+	+	+	-	+
Liu[62]	2021	BPD, D6, LUS score + clinical data	+	+	+	-	+	+	+	-	+
		BPD, D9, LUS score + clinical data	+	+	+	-	+	+	+	-	+
		BPD, D6, LUS score + clinical data	+	+	+	-	+	+	+	-	+
		BPD, D9, LUS score + clinical data	+	+	+	-	+	+	+	-	+
		BPD, D6, LUS score + clinical data	+	+	+	-	+	+	+	-	+
		BPD, D9, LUS score + clinical data	+	+	+	-	+	+	+	-	+

(continued)

Table III. Continued

Study	Year	Model description (outcome, timing, type of predictors)	RoB				Applicability			Overall	
			Participants	Predictors	Outcome	Analysis	Participants	Predictors	Outcome	RoB	Applicability
Mohamed[63]	2021	BPD, D3, clinical data	+	+	?	-	?	+	+	-	+
		BPD, D7, clinical data	+	+	?	-	?	+	+	-	+
		BPD, D14, clinical data	+	+	?	-	?	+	+	-	+
		BPD, D3, LUS score + clinical data	+	+	?	-	?	+	+	-	+
		BPD, D7, LUS score + clinical data	+	+	?	-	?	+	+	-	+
		BPD, D14, LUS score + clinical data	+	+	?	-	?	+	+	-	+
Shim[64]	2021	BP D0, clinical data	+	+	+	-	+	+	+	-	+
		BP D0, clinical data	+	+	+	-	+	+	+	-	+
Song[65]	2021	Death/BPD, D7, clinical data	+	+	+	?	+	+	+	-	+
		Death/BPD, D7, blood biomarkers + clinical data	+	+	+	?	+	+	+	-	+
Soullane[66]	2021	BPD, D10, clinical data	+	+	?	-	+	+	+	-	+
Ushida[67]	2021	BPD, D0, clinical data	+	+	+	-	+	+	+	-	+
Woods[68]	2021	Death/BPD, D1, LUS score + clinical data	+	+	+	-	+	+	+	-	+
		Death/BPD, D3, LUS score + clinical data	+	+	+	-	+	+	+	-	+
		Death/BPD, D7, LUS score + clinical data	+	+	+	-	+	+	+	-	+
Zhang[69]	2021	BPD, D3, clinical data	+	+	+	-	+	+	+	-	+
		BPD, D7, clinical data	+	+	+	-	+	+	+	-	+
		BPD, D14, clinical data	+	+	+	-	+	+	+	-	+
Sharma[54]	2020	BPD, D14, clinical data	+	-	+	-	+	+	+	-	+
Alvarez-Fuente[51]	2019	BPD, D7, echocardiographic data	+	+	+	-	?	?	+	-	?
		BPD, D7, echocardiographic data + blood biomarkers	+	+	+	-	?	?	+	-	?

(*continued*)

Table III. Continued

Study	Year	Model description (outcome, timing, type of predictors)	RoB				Applicability			Overall	
			Participants	Predictors	Outcome	Analysis	Participants	Predictors	Outcome	RoB	Applicability
Beltempo[50]	2019	BPD, H12, clinical data	+	+	?	-	+	+	+	-	+
		BPD, H12, clinical data	+	+	?	-	+	+	+	-	+
		BPD, H12, clinical data	+	+	?	-	+	+	+	-	+
Fairchild[49]	2019	Death/BPD, D7, clinical data	+	+	+	-	+	+	+	-	+
		Death/BPD, D7, clinical + monitoring data	+	+	+	-	+	+	+	-	+
Valenzuela-Stutman[46]	2019	BPD, D1, clinical data	+	+	+	-	+	+	+	-	+
		Death/BPD, D1, clinical data	+	+	+	-	+	+	+	-	+
		BPD, D3, clinical data	+	+	+	-	+	+	+	-	+
		Death/BPD, D3, clinical data	+	+	+	-	+	+	+	-	+
		BPD, D7, clinical data	+	+	+	-	+	+	+	-	+
		Death/BPD, D7, clinical data	+	+	+	-	+	+	+	-	+
		BPD, D14, clinical data	+	+	+	-	+	+	+	-	+
		Death/BPD, D14, clinical data	+	+	+	-	+	+	+	-	+
Veneroni[45]	2019	BPD, D1, lung mechanics	+	+	+	-	-	+	+	-	-
Bentsen[44]	2018	BPD, D2, ventilator data	+	+	+	-	-	+	+	-	-
Boghossian[43]	2018	BPD, at birth, clinical data	+	+	-	-	?	-	?	-	-
Sullivan[41]	2018	BPD, D7, clinical data	+	+	+	-	+	-	+	-	-
		BPD, D7, monitoring data	+	+	+	-	+	?	+	-	?
		BPD, D7, clinical + monitoring data	+	+	+	-	+	-	+	-	-
Kandasamy[40]	2017	Death/BPD, unclear, cord blood biomarkers	+	+	+	-	+	-	+	-	+
		Death/BPD, unclear, cord blood biomarkers	+	+	+	-	+	-	+	-	+

(*continued*)

Table III. Continued

Study	Year	Model description (outcome, timing, type of predictors)	RoB				Applicability			Overall	
			Participants	Predictors	Outcome	Analysis	Participants	Predictors	Outcome	RoB	Applicability
Wai[37]	2016	Death/BPD, D14, clinical data	+	+	+	-	-	?	+	-	-
El-Khuffash[36]	2015	Death/BPD, D2, echocardiographic data	+	+	+	-	+	?	+	-	?
Kandasamy[35]	2015	Death/BPD, D1, cord blood biomarkers	+	+	+	-	+	+	+	-	+
Popova[34]	2015	Death/BPD, unclear, tracheal biomarkers	?	?	+	-	-	?	+	-	-
Schneibel[32]	2013	BPD, D1, tracheal biomarkers	+	+	+	-	-	?	+	-	-
Ambalavanan[30]	2011	Death/BPD, D7, clinical data	?	+	+	-	+	+	+	-	+
Laughon[28]	2011	Death/BPD, D1, clinical data	+	+	-	-	+	+	+	-	+
		Death/BPD, D3, clinical data	+	+	-	-	+	+	+	-	+
		Death/BPD, D7, clinical data	+	+	-	-	+	+	+	-	+
		Death/BPD, D14, clinical data	+	+	-	-	+	+	+	-	+
Messershmidt[27]	2011	BPD, D1, clinical data	+	+	+	-	-	+	+	-	-
Subramanian[26]	2011	BPD, D6, clinical data	+	?	+	-	+	?	+	-	?
Ambalavanan[25]	2008	Death/BPD, unclear, clinical data	-	+	+	-	-	+	+	-	-
		Death/BPD, unclear, clinical data	-	+	+	-	-	+	+	-	-
Choi[23]	2006	BPD, unclear, tracheal biomarkers	+	-	+	-	-	?	-	-	-
Henderson-Smart[22]	2006	BPD, at birth, clinical data	+	+	+	-	+	+	+	-	+
Kim[21]	2005	BPD, D4, clinical data	+	+	+	-	+	+	+	-	+
		BPD, D7, clinical data	+	+	+	-	+	+	+	-	+
		BPD, D10, clinical data	+	+	+	-	+	+	+	-	+
Ng[19]	2004	Death/BPD, D14, blood biomarkers	+	-	+	-	-	-	+	-	-
Chien[18]	2002	BPD, H12, clinical data	+	+	+	-	+	+	+	-	+
		BPD, H12, clinical data	+	+	+	-	+	+	+	-	+

(*continued*)

Table III. Continued

Study	Year	Model description (outcome, timing, type of predictors)	RoB				Applicability			Overall	
			Participants	Predictors	Outcome	Analysis	Participants	Predictors	Outcome	RoB	Applicability
Lui[17]	2000	BPD, unclear, lung mechanics	+	+	+	-	-	?	+	-	-
		BPD, unclear, clinical data	+	+	+	-	-	+	+	-	-
Yoder[16]	1999	Death/BPD, H12, clinical data	-	+	+	-	-	+	-	-	-
		Death/BPD, D3, clinical data	-	+	+	-	-	+	-	-	-
Subhedar[14]	1998	Death/BPD, D1, echocardiographic data	+	+	+	-	-	+	+	-	-
		Death/BPD, D1, clinical data	+	+	+	-	-	+	+	-	-
Ryan[13]	1996	BPD, D4, clinical data	+	?	-	-	-	?	-	-	-
Validated models											
Alonso-Ojembarrena[71]	2022	BPD, D1, LUS score	+	+	+	-	+	+	+	-	+
		BPD, D3, LUS score	+	+	+	-	+	+	+	-	+
		BPD, D7, LUS score	+	+	+	-	+	+	+	-	+
		BPD, D14, LUS score	+	+	+	-	+	+	+	-	+
Aldecoa-Bilbao[57]	2021	BPD, D7, LUS score	+	+	+	-	+	+	+	-	+
Alonso-Ojembarrena[52]	2021	BPD, D3, LUS score	+	+	+	-	+	+	+	-	+
		BPD, D3, modified LUS score	+	+	+	-	+	+	+	-	+
		BPD, D7, LUS score	+	+	+	-	+	+	+	-	+
		BPD, D7, modified LUS score	+	+	+	-	+	+	+	-	+
		BPD, D14, LUS score	+	+	+	-	+	+	+	-	+
		BPD, D14, modified LUS score	+	+	+	-	+	+	+	-	+
Baud[58]	2021	Death/BPD, at birth, NICHD model	+	+	+	+	+	+	+	+	+
Bhattacharjee[56]	2021	BPD, D3, RSS	+	+	?	-	-	+	+	-	-
Gerull[60]	2021	Death/BPD, D7, NICHD model	+	+	+	-	+	+	+	-	+
Liu[62]	2021	BPD, D1, LUS score	+	+	+	-	+	+	+	-	+

(*continued*)

Table III. Continued

Study	Year	Model description (outcome, timing, type of predictors)	RoB				Applicability			Overall	
			Participants	Predictors	Outcome	Analysis	Participants	Predictors	Outcome	RoB	Applicability
		BPD, D2, LUS score	+	+	+	-	+	+	+	-	+
		BPD, D3, LUS score	+	+	+	-	+	+	+	-	+
		BPD, D6, LUS score	+	+	+	-	+	+	+	-	+
		BPD, D9, LUS score	+	+	+	-	+	+	+	-	+
		BPD, D12, LUS score	+	+	+	-	+	+	+	-	+
		BPD, D1, modified LUS score	+	+	+	-	+	+	+	-	+
		BPD, D2, modified LUS score	+	+	+	-	+	+	+	-	+
		BPD, D3, modified LUS score	+	+	+	-	+	+	+	-	+
		BPD, D6, modified LUS score	+	+	+	-	+	+	+	-	+
		BPD, D9, modified LUS score	+	+	+	-	+	+	+	-	+
		BPD, D12, modified LUS score	+	+	+	-	+	+	+	-	+
		BPD, D1, modified LUS score	+	+	+	-	+	+	+	-	+
		BPD, D2, modified LUS score	+	+	+	-	+	+	+	-	+
		BPD, D3, modified LUS score	+	+	+	-	+	+	+	-	+
		BPD, D6, modified LUS score	+	+	+	-	+	+	+	-	+
		BPD, D9, modified LUS score	+	+	+	-	+	+	+	-	+
		BPD, D12, modified LUS score	+	+	+	-	+	+	+	-	+
Mohamed[63]	2021	BPD, D3, LUS score	+	+	?	-	?	+	+	-	?
		BPD, D7, LUS score	+	+	?	-	?	+	+	-	?
		BPD, D14, LUS score	+	+	?	-	?	+	+	-	?
Shim[64]	2021	BPD, D0, clinical data	+	+	+	-	+	+	+	-	+
		BPD, D0, clinical data	+	+	+	-	+	+	+	-	+

(*continued*)

Table III. Continued

Study	Year	Model description (outcome, timing, type of predictors)	RoB				Applicability			Overall	
			Participants	Predictors	Outcome	Analysis	Participants	Predictors	Outcome	RoB	Applicability
Ushida[67]	2021	BPD, D0, clinical data	+	+	+	-	+	+	+	-	+
Woods[68]	2021	BPD, D1, modified LUS score	+	+	+	-	+	+	+	-	+
		BPD, D3, modified LUS score	+	+	+	-	+	+	+	-	+
		BPD, D7, modified LUS score	+	+	+	-	+	+	+	-	+
		BPD, D1, modified LUS score	+	+	+	-	+	+	+	-	+
		BPD, D3, modified LUS score	+	+	+	-	+	+	+	-	+
		BPD, D7, modified LUS score	+	+	+	-	+	+	+	-	+
Bhattacharjee[56]	2020	BPD, unclear, RSS score	?	+	+	-	-	+	+	-	-
Oulego-Erroz[55]	2020	BPD, D7, LUS score	+	+	+	-	+	+	+	-	+
Sotodate[53]	2020	BPD, H1, CRIB score	+	+	+	-	+	+	+	-	+
		BPD, D1, SNAP-II score	+	+	+	-	+	+	+	-	+
		BPD, H12, SNAPPE-II score	+	+	+	-	+	+	+	-	+
Alonso-Ojembarrena[52]	2019	BPD, D1, LUS score	+	+	+	-	+	+	+	-	+
		BPD, D3, LUS score	+	+	+	-	+	+	+	-	+
		BPD, D7, LUS score	+	+	+	-	+	+	+	-	+
		BPD, D14, LUS score	+	+	+	-	+	+	+	-	+
Beltempo[50]	2019	BPD, H12, SNAPPE-II score	+	+	?	-	+	+	+	-	+
		BPD, H12, SNAPPE-II score	+	+	?	-	+	+	+	-	+
Jung[48]	2019	Death/BPD, D7, RSS score	-	+	+	-	-	+	+	-	-
Lee[47]	2019	BPD, H1, CRIB-II score	+	+	+	-	+	+	+	-	+
		BPD, H1, CRIB-II score	+	+	+	-	+	+	+	-	+

(*continued*)

Table III. Continued

Study	Year	Model description (outcome, timing, type of predictors)	RoB				Applicability			Overall	
			Participants	Predictors	Outcome	Analysis	Participants	Predictors	Outcome	RoB	Applicability
Gulliver[42]	2018	Death/BPD, D7, NICHD model	+	+	?	-	+	+	?	-	?
		Death/BPD, D14, NICHD model	+	+	?	-	+	+	?	-	?
Özcan[39]	2017	BPD, H12, SNAPPE-II score	+	+	+	-	+	+	+	-	+
Sullivan[38]	2016	BPD, D1, monitoring data	-	+	+	-	+	+	+	-	+
		BPD, D7, monitoring data	-	+	+	-	+	+	+	-	+
		BPD, H12, SNAP-II score	-	+	+	-	+	+	+	-	+
		BPD, H12, CRIB-II score	-	+	+	-	+	+	+	-	+
Truog[33]	2014	Death/BPD, D7, NICHD model	+	+	?	-	+	+	+	-	+
		Death/BPD, D14, NICHD model	+	+	?	-	+	+	+	-	+
Sehgal[31]	2013	BPD, unclear, echocardiographic data	-	-	+	-	-	?	+	-	-
Ambalavanan[30]	2011	Death/BPD, D7, clinical data	?	+	+	-	+	+	+	-	+
Carvalho[29]	2011	BPD, H12, SNAPPE-II score	+	+	+	-	-	+	+	-	-
Laughon[28]	2011	Death/BPD, D1, NICHD model	+	+	-	-	+	+	+	-	+
		Death/BPD, D1, NICHD model	+	+	-	-	+	+	+	-	+
		Death/BPD, D3, NICHD model	+	+	-	-	+	+	+	-	+
		Death/BPD, D3, NICHD model	+	+	-	-	+	+	+	-	+
		Death/BPD, D7, NICHD model	+	+	-	-	+	+	+	-	+
		Death/BPD, D7, NICHD model	+	+	-	-	+	+	+	-	+
		Death/BPD, D14, NICHD model	+	+	-	-	+	+	+	-	+
		Death/BPD, D14, NICHD model	+	+	-	-	+	+	+	-	+
May[24]	2007	BPD, D2, Madan score	+	+	+	-	-	+	+	-	-

(*continued*)

Table III. Continued

Study	Year	Model description (outcome, timing, type of predictors)	RoB				Applicability			Overall	
			Participants	Predictors	Outcome	Analysis	Participants	Predictors	Outcome	RoB	Applicability
		BPD, D2, Madan score	+	+	+	-	-	+	+	-	-
		BPD, D7, Madan score	+	+	+	-	-	+	+	-	-
		BPD, D7, Madan score	+	+	+	-	-	+	+	-	-
Henderson-Smart[22]	2006	BPD, at birth, clinical data	+	+	+	-	+	+	+	-	+
Kim[21]	2005	BPD, D4, clinical data	+	+	+	-	+	+	+	-	+
		BPD, D7, clinical data	+	+	+	-	+	+	+	-	+
		BPD, D10, clinical data	+	+	+	-	+	+	+	-	+
		BPD, D4, Yoder score	+	+	+	-	+	+	+	-	+
		BPD, D7, Yoder score	+	+	+	-	+	+	+	-	+
		BPD, D10, Yoder score	+	+	+	-	+	+	+	-	+
Greenough[20]	2004	BPD, D7, Chest radiograph score	+	+	+	-	-	+	+	-	-
		BPD, D7, Chest radiograph score	+	+	+	-	-	+	+	-	-
Chien[18]	2002	BPD, H12, SNAP score	+	+	+	-	+	+	+	-	+
		BPD, H12, SNAP-II score	+	+	+	-	+	+	+	-	+
Yoder[16]	1999	Death/BPD, H12, Yoder score	+	+	+	-	?	+	-	-	-
		Death/BPD, D3, Yoder score	+	+	+	-	?	+	-	-	-
		Death/BPD, H12, Sinkin score	-	+	+	-	-	+	-	-	-
		Death/BPD, D3, Ryan score	-	+	+	-	-	+	-	-	-
Hentschel[15]	1998	BPD, H12, Sinkin score	+	+	+	-	+	+	+	-	+
		Death/BPD, H12, Sinkin score	+	+	+	-	+	+	+	-	+
		BPD, D10, Sinkin score	+	+	+	-	+	+	+	-	+
		Death/BPD, D10, Sinkin score	+	+	+	-	+	+	+	-	+

(*continued*)

Table III. Continued

Study	Year	Model description (outcome, timing, type of predictors)	RoB				Applicability			Overall	
			Participants	Predictors	Outcome	Analysis	Participants	Predictors	Outcome	RoB	Applicability
		BPD, H12, CRIB score	+	+	+	-	+	+	+	-	+
		Death/BPD, H12, CRIB score	+	+	+	-	+	+	+	-	+
		BPD, at admission, Berlin score	+	+	+	-	+	+	+	-	+
		Death/BPD, at admission, Berlin score	+	+	+	-	+	+	+	-	+
Subhedar[14]	1998	Death/BPD, D1, echocardiographic data	+	+	+	-	-	+	+	-	-
		Death/BPD, D1, clinical data	+	+	+	-	-	+	+	-	-
Ryan[13]	1996	BPD, D4, clinical data	?	?	-	-	?	?	-	-	-

BP, blood pressure; *CRIB*, Clinical Risk Index for Babies; *LUS*, lung ultrasound; *NICHD, Eunice Kennedy Shriver* National Institute of Child Health and Human Development *RoB*, risk of bias; *SNAP*, Score for Neonatal Acute Physiology; *SNAPPE*, Score for Neonatal Acute Physiology Perinatal Extension.
+ = low ROB/low concern regarding applicability/ - = high ROB/high concern regarding applicability/ ? = unclear ROB/unclear concern regarding applicability.

have been developed, and none have undergone external validation.[52,55] Aside from the potential difficulties in assessing these variables in daily clinical practice, the highlighted pitfalls prevent conclusions about the potential usefulness of prediction models using biomarkers or lung ultrasound data in daily care. In addition, most studies used a single center, which limits the generalizability of the developed and/or validated prediction model. The prediction models with the best 3 discriminating performances showed a c-statistic between 0.97 and 1.00, although there is a risk that these models are overfit. These models included predictors regarding lung mechanics, lung imaging and echocardiographic data, and used logistic regression analysis for model development with timing of model assessment in the first week of life. All models had a low sample size with low events per variable, which probably influence the high c-statistic, and 2 models reported the final model including intercept and predictor weights.[63,74] However, none of these models were internally or externally validated, and although one model presented the calibration performance with pseudo-R^2, none reported a calibration plot.[45] Given these flaws, these models have an increased risk of bias, despite their promising discrimination performances. The best three discriminating externally validated models reported c-statistics between 0.96 and 0.97, which also indicates good discrimination.[13,21,63] However, all models had insufficient sample sizes to perform adequate external validation, and no calibration performances were reported. Although these 3 studies showed promising discriminating performances, none of these models can be recommended for implementation in clinical care due to methodologic flaws.

A strength of this review is our meta-analysis provided a quantification of the overall performances, including a PI and heterogeneity of the models. Meta-analysis of the c-statistic of all validated models for the outcome BPD and death/BPD revealed good performance (0.77 and 0.82, respectively). Subsequently, meta-analysis combining models per time point showed an increase in the pooled c-statistic from the validated models for the outcome BPD and death/BPD after the first week of life. This finding is in line with the pathophysiological understanding that BPD is a developing disease during the neonatal period, and future research should investigate whether dynamic models using different predictors over time improve BPD prediction. The calculated PIs indicate that the validated models in the second week of life can perform very differently in a new set of infants, indicating that updating is necessary.[83]

This review has some limitations. We were unable to perform external validation of the identified prediction models due to frequent inadequate reporting of final prediction model. In addition, we found no dataset that fulfilled all the requirements to perform validation. The ideal dataset should have a sufficient sample size, with a population-based recruitment of infants born very preterm to limit the risk of selection bias, and contain all the predictors needed to apply the prediction models, including detailed

information on respiratory management, biomarkers that are not routinely collected and imaging data.

In conclusion, many different BPD prediction models have satisfactory performance. However, their actual value in clinical practice remains uncertain as the result of methodologic issues, lack of external validation, and no calibration assessment. Adherence to existing reporting and methodologic guidelines are needed to improve the quality of research on prediction modeling. Future research should aim to validate externally existing models in different countries, assess both discrimination and calibration performances, and conduct impact studies. ■

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